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## Medical Policy



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**\*Current Policy Effective Date: 11/1/23**  
(See policy history boxes for previous effective dates)

### **Title: Remote Electrical Neuromodulation for Migraines**

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#### **Description/Background**

##### **Remote Electrical Neuromodulation**

Nonpharmacologic remote electrical neuromodulation (REN) has been proposed as an alternative to pharmacologic interventions for patients with migraine and as a way to decrease the use of abortive medications and the risk of medication overuse in the treatment of migraine headaches.

The REN device Nerivio™ was cleared for use by the Food and Drug Administration in 2019. It is worn on the upper arm and stimulates the peripheral nerves to induce conditioned pain modulation. The conditioned pain in the arm induced by the Nerivio device is purported to reduce the perceived migraine pain intensity.(6) Control of the device is accomplished through Bluetooth communication between the device and the patient's smartphone or tablet. 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. Patient-controlled stimulation intensity ranges from 0 to 100%, corresponding to 0 to 40 milliamperes (mA) of electrical current. Patients are instructed to set the device to the strongest stimulation intensity that is just below their perceived pain level. The device provides stimulation for up to 45 minutes before turning off automatically. The Nerivio manufacturer indicates that the device can be used instead of or in addition to medication.

##### **Migraine**

Migraine is a neurologic disease characterized by recurrent moderate to severe headaches with associated symptoms that can include aura, photophobia, nausea, and/or vomiting.(1) Overall migraine prevalence in the United States is about 15% but varies according to population group.(2) Prevalence is higher in women (21%), among American Indian/Alaska Natives (22%), and among 18- to 44-year-olds (19%). Social determinants including low education level (18%), use of Medicaid (27%), high poverty level (23%), and being unemployed (22%) are also associated with higher rates of migraine.

Migraine is categorized as episodic or chronic depending on the frequency of attacks. Generally, episodic migraine is characterized by 14 or fewer headache days per month and chronic migraine is characterized by 15 or more headache days per month.(3) Specific International Classification of Headache Disorders<sup>4</sup> diagnostic criteria are as follows:

- Episodic migraine:
  1. Untreated or unsuccessfully treated headache lasting 4 to 72 hours.
  2. Headache has at least 2 of the following characteristics:
    - a. Unilateral location
    - b. Pulsating quality
    - c. Moderate or severe pain intensity
    - d. Aggravation by or causing avoidance of routine physical activity.
  3. At least 1 of the following during headache:
    - a. Nausea and/or vomiting.
    - b. Photophobia or phonophobia.
- Chronic migraine:
  1. Migraine-like or tension-type headache on 15 or more days per month for more than 3 months
  2. At least 5 headache attacks without aura meet episodic migraine criteria 1 to 3, and/or at least 5 headache attacks with aura meet episodic migraine criteria 2 to 3.
  3. On more than 8 days per month for more than 3 months, fulfilling any of the following criteria:
    - a. For migraine without aura, episodic migraine criteria 2 and 3
    - b. For migraine with aura, episodic migraine criteria 1 and 2
    - c. Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative.

Migraine attacks, whether due to episodic or chronic migraine, require acute management. The goal of acute treatment is to provide pain and symptom relief as quickly as possible while minimizing adverse effects, with the intent of timely return to normal function. Pharmacologic interventions for treatment of acute migraine vary according to migraine severity. First-line therapy for an acute episode of mild or moderate migraine includes oral non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen. Moderate to severe migraine can be treated through the use of triptans or an NSAID-triptan combination. Antiemetics can be added for migraine accompanied by nausea or vomiting, though certain antiemetic medications used as monotherapy can also provide migraine relief. Other pharmacologic interventions used to treat acute migraine include calcitonin-gene related peptide antagonists, which can be used in patients with an insufficient response or contraindications to triptans, lasmiditan, and dihydroergotamine. Migraine can be managed at home, although acute migraine is a frequently cited reason for primary care and emergency department visits.(5) Regular use of pharmacologic interventions can result in medication overuse, which in turn could lead to rebound headache and increased risk of progression from episodic to chronic migraine.(4)

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## Regulatory Status

In May 2019, Nerivio Migra™ (Theranica Bio-Electronics Ltd.) was granted a de novo classification by the FDA (class II, special controls, product code: QGT).(7) This new classification applied to this device and substantially equivalent devices of this generic type. Nerivio Migra was initially cleared for treatment of acute migraine in adults who do not have chronic migraine.

In October, 2020, Nerivio was cleared for marketing by the FDA through the 510(k) process (K201824). FDA determined that this device was substantially equivalent to Nerivio Migra for use in adults.(8) The device name changed to just “Nerivio” and the exclusion of chronic migraine patients was removed. The Nerivio device can provide more treatments than the predicate Nerivio Migra (12 treatments vs. 8 treatments) and has a longer shelf life (24 months vs. 9 months). In January, 2021, the Nerivio device was cleared for use in patients aged 12 to 17 years.(9)

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## Medical Policy Statement

Remote electrical neuromodulation for the treatment of migraines is considered experimental/investigational. There is insufficient evidence to determine if the technology is an improvement on existing therapies.

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## Inclusionary and Exclusionary Guidelines

N/A

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**CPT/HCPCS Level II Codes** *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

### **Established codes:**

N/A

### **Other codes (investigational, not medically necessary, etc.):**

K1023

E1399

*Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.*

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## Rationale

### ACUTE MIGRAINE ATTACK DUE TO EPISODIC OR CHRONIC MIGRAINE

#### Clinical Context and Therapy Purpose

The purpose of remote electrical neuromodulation (REN) in patients who have acute migraine attacks due to episodic or chronic migraine is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

#### Populations

The relevant population of interest is individuals with acute migraine due to episodic or chronic migraine.

#### Interventions

The therapy being considered is REN with the Nerivio device.

#### Comparators

The following therapies are currently being used to treat acute migraine due to episodic or chronic migraine: medical management or no treatment. A number of medications are used to treat migraine. First-line therapy for mild or moderate migraine includes oral non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen. More severe migraine can be treated through the use of triptans or an NSAID-triptan combination through a variety of routes (e.g., oral, nasal spray or powder, subcutaneous). Antiemetics can be added for migraine accompanied by nausea or vomiting. Other pharmacologic interventions used to treat acute migraine include calcitonin-gene related peptide antagonists, which can be used in patients with an insufficient response or contraindications to triptans, lasmiditan, and dihydroergotamine.

#### Outcomes

The general outcomes of interest are: symptoms, functional outcomes, quality of life, and treatment-related morbidity. Specific important health outcomes include freedom from migraine pain and bothersome symptoms, restored function (e.g., return to normal activities), and patient-assessed global impression of treatment. Examples of relevant outcome measures appear in Table 1.

Follow-up over several hours is needed to monitor for treatment effects.

**Table 1. Health Outcome Measures Relevant to Acute Migraine Attack (3,10,11)**

Outcome	Description
Pain free	No pain at defined assessment time (e.g., 2 hours)
Pain relief	Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time (e.g., 2 hours)
Sustained pain free	No pain at initial assessment (e.g., 2 hours) and remains at follow-up assessment (e.g., 1 day) with no use of rescue medication or relapse (recurrence) within that time frame
Sustained pain relief	Improvement of pain from moderate to severe at baseline to mild or none or pain scale improved at least 50% from baseline at defined assessment time (e.g., 2 hours) and remains

	improved at follow-up assessment (e.g., 1 day) with no use of rescue medication or relapse (recurrence) within that time frame
Symptom relief	Improvement of most bothersome symptom(s) from moderate to severe at baseline to mild or none at defined assessment time (e.g., 2 hours)
Function relief	Improvement of function from moderate to severe at baseline to mild or none at defined assessment time (e.g., 2 hours)
Restored function	No restriction to perform work or usual activities at a defined assessment time (e.g., 2 hours)
Global impact of treatment	Patient assessment of functional disability and health-related quality of life using a Likert or other validated scale at a defined assessment time (e.g., 2 hours)
Global evaluation of treatment	Patient assessment of overall treatment effect (pain, symptom relief, adverse events) using a Likert or other validated scale at a defined assessment time (e.g., 2 hours)

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Consistent with a 'best available evidence approach,' within each category of study design, studies with larger sample sizes and longer durations were sought;
- Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

### Randomized Controlled Trials

Use of REN for the treatment of migraine has been assessed in 2 RCTs (Yarnitsky et al, 2017[12] and 2019[13]) comparing an active REN device (Nerivio Migra) with a sham device in patients with an acute migraine attack due to episodic migraine.

A pilot, crossover trial conducted by Yarnitsky et al (2017) included data from 71 (of 86 randomized) patients who received active or sham REN.(12) All patients were given an identical REN device that was preprogrammed to deliver in random order 4 active treatment sessions ranging from 80 to 120 hertz (Hz), corresponding to pulse widths of 50 to 200 milliseconds, and 1 sham session of 0.1 hertz (45 millisecond pulse width). Both active and sham treatments were programmed for a duration of 20 minutes each. Most patients were women (80%) in their mid-40s (mean age: 46 years), with a mean of 5 migraine attacks per month with a mean pain intensity of 8.8, corresponding to severe pain. Race and/or ethnicity were not reported. In the trial, treatment with active REN was more frequently associated with reduction in, and freedom from, migraine pain than sham REN at 2-hour follow-up (Table 3). When the device was programmed to deliver an active treatment session, it was most effective at reducing pain when used within 20 minutes of migraine onset. Treatment response to active REN diminished over time of initiation following migraine onset, and no active REN participants reported complete pain relief if the device was initiated more than 1 hour from onset. No adverse events were reported, though patients were more likely to rate their treatment perception of the active REN sessions as painful (11%) or unpleasant (28%) compared with

sham REN sessions (1% painful; 13% unpleasant). Other outcomes were not reported in this study. Study limitations appear in Tables 4 and 5.

A second, larger (N=252) RCT was conducted by Yarnitsky et al in 2019 (Table 2).<sup>(13)</sup> The mean age of study participants was 43 years, 81% were female. Most participants were of White race (88%); 7% were Black and less than 1% were Asian. Time since migraine diagnosis was not reported; participants experienced a mean of 7 migraine days per month. Seventy-one percent of participants managed migraines with the use of acute medication, but important details about type and dosage were not provided. At baseline, 50% of participants reported that light sensitivity was their most bothersome symptom apart from migraine pain, followed by nausea (27%) and sound sensitivity (19%). After a 2 to 4-week run-in during which study participants kept a headache diary, participants were randomized to 4 to 6 weeks of at-home active or sham REN. The frequency was 100 to 120 Hz for the active device and less than 0.1 Hz for the sham device. The pulse width was 400 microseconds for the active device and ranged from 40 to 550 microseconds for the sham device, with the intent of mimicking a similar sensation as that delivered by the active device. At the time of randomization, participants were instructed on how to determine their optimal REN intensity, but this was unclearly defined as a threshold that was "perceptible not painful" (e.g., no specific measure of intensity was described) and no data on the actual intensities used during the study were reported. Participants were instructed to treat their migraine with the REN device as soon as possible following migraine onset, and no later than within 1 hour of onset. Participants who initiated device use more than 1 hour following onset were excluded from the outcome analyses. Study results are summarized in Table 3. Patients treated with active REN were more likely to report freedom from pain and pain relief at 2-hour follow-up, and sustained freedom from pain and pain relief at 48-hour follow-up compared with the sham REN group. There was no statistical between-group difference in the proportions of patients reporting freedom from their most bothersome symptom (MBS) at 2-hour follow-up, but a greater proportion of active REN patients reported MBS relief at 2 hours relative to sham REN. Device-related adverse events were reported in 5% of active REN and 2% of sham REN participants (p=.49). At the conclusion of the study, participants were asked whether they believed they had received active or sham treatment as a measure of blinding. Half as many active participants correctly identified their device as did sham participants (23% in the active group vs. 50% in the sham group), although statistical analyses determined the treatment outcome differences between groups were not affected by participants perceived treatment group. Relevance and methodological limitations of the study are detailed in Tables 4 and 5. Notable limitations include an unclearly defined intended use population, a non-empirically determined optimum treatment regimen, and no assessment of functional or quality of life outcomes.

**Table 2. Summary of Key RCT Characteristics**

Study;						
Trial	Countries	Sites	Dates	Participants	Interventions	
Yarnitsky et al (2017) <sup>12</sup> .	Israel	1	2016-2016	Adults (18 to 75 years) with ICHD-3 migraine 2 to 8 days/month with no preventive medication use 2 months prior to enrollment	Active n=86 Active REN device; 4/5 preprogrammed treatment sessions	Comparator NA; crossover trial Sham REN device; 1/5 preprogrammed treatment sessions

Yarnitsky et al (2019) <sup>13</sup> .	US, Israel	12	2017-2018	Adults (18 to 75 years) with ICHD-3 migraine 2 to 8 days/month but <12 days/month, with no or stable preventive medication use 2 months prior to enrollment	n=126 Active REN (Nerivio) device	n=126 Sham REN device
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ICHHD: International Classification of Headache Disorders; RCT: randomized controlled trial; REN: remote electrical neuromodulation.

**Table 3. Summary of Key RCT Results**

Study	Pain Free <sup>1</sup> , 2 hours	Pain Relief <sup>2</sup> , 2 hours	Sustained Pain Free, 48 hours	Sustained Pain Relief, 48 hours	MBS Free, 2 hours	MBS Relief <sup>3</sup> , 2 hours
<b>Yarnitsky et al (2017)<sup>12</sup>.</b>						
Active REN	44.1% (19/43)	76.7% (33/43)	NR	NR	NR	NR
Sham REN	5.9% (1/17)	23.5% (4/17)	NR	NR	NR	NR
p value	.005	.005	NR	NR	NR	NR
<b>Yarnitsky et al (2019)<sup>13</sup>.</b>						
Active REN	37.4% (37/99)	66.7% (66/99)	20.7% (18/87)	39.1% (34/87)	40.7% (33/81)	46.3% (44/95)
Sham REN	18.4% (19/103)	38.8% (40/103)	7.9% (7/89)	16.9% (15/89)	36.4% (32/88)	22.2% (22/99)
p value	.003	<.001	.014	.001	.55	.001

MBS: most bothersome symptom; NR: not reported; RCT: randomized controlled trial; REN: remote electrical neuromodulation.

<sup>1</sup> Change in headache severity from mild, moderate, or severe at baseline, to none.

<sup>2</sup> Change in headache severity from moderate, or severe at baseline, to none or mild, or a reduction in headache severity from mild to none.

<sup>3</sup> Subjective (undefined) relief of most bothersome symptom.

**Table 4. Study Relevance Limitations**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Duration of Follow-up <sup>e</sup>
Yarnitsky et al (2017) <sup>12</sup> .	1, 2 Intended use population is unclear (e.g., treatment naïve, those with contraindications to medication, or those who have failed pharmacologic treatment); time since migraine diagnosis and details about current migraine management regimen not reported		2 Comparison versus an acute treatment with established efficacy would be preferred	1, 5 Functional and quality of life outcome measures not addressed	
Yarnitsky et al (2019) <sup>13</sup> .	1, 2 Intended use population is unclear (e.g., treatment naïve, those with contraindications to medication, or those who have failed	1, 5 Details about the mean timing of device initiation and mean, recommended or optimal device	1, 2 Details and subgroup analysis on the effect of preventive medication use in 29% of active and	1, 5 Functional and quality of life outcome measures	

pharmacologic treatment); time since migraine diagnosis and details about current migraine management regimen not reported	intensity (in mA) were not reported; a clinically relevant device intensity threshold has not been established	37% of sham participants were not reported; comparison versus an acute treatment with established efficacy would be preferred	not addressed
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The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.

<sup>b</sup> Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5. Other.

<sup>c</sup> Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.

<sup>d</sup> Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

**Table 5. Study Design and Conduct Limitations**

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Yarnitsky et al (2017) <sup>12</sup> .	3 Method of allocation to active or sham treatment session not reported			1 No data reported for 17% (15/86) of enrolled participants	1 This was a pilot study; no sample size rationale or power calculations were reported	
Yarnitsky et al (2019) <sup>13,7</sup> .				1 19% (49/252) of randomized participants not accounted for in analysis described as intention to treat		

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias; 5. Other.

<sup>b</sup> Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.

<sup>d</sup> Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials); 7. Other.

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.

<sup>f</sup> Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated; 5. Other.

Avoiding medication overuse has been postulated as a potential benefit of REN treatment of acute migraine. Marmura et al (2020)(14) reported the results of an observational 8-week open-label extension study following the double-blind phase of the Yarnitsky 2019 trial. The Marmura study compared within-subject data (N=117) from the trial run-in phase with data from the open-label phase, finding that a higher proportion of patients avoided medication use during the open-label phase (when the REN device was available for use; 89.7%) than in the run-in phase (when the REN device was not available for use; 15.4%). Although these results



suggest that use of the REN device could result in less medication use and therefore reduce the risk of medication overuse, confirmatory studies designed to directly assess the role of REN in populations at risk of medication overuse are needed.

A post-hoc analysis of the Yarnitsky 2019 RCT retrospectively compared the effectiveness of acute migraine treatment with the Nerivio device with usual care (i.e., pharmacologic acute migraine management) used during the 2- to 4-week run-in phase of the trial.<sup>(15)</sup> Pharmacologic treatment used during the run-in phase consisted of NSAIDs, acetaminophen (alone, or in combination with aspirin and caffeine) or triptans. In analysis of a subset of 99 trial participants, the rate of freedom from pain was similar for Nerivio (37.4% [37/99]) and usual care (26.3% [26/99]; p=.099) at 2-hour follow-up. Results were similar for achievement of pain relief (66.7% [66/99] vs. 52.5% [52/99]; p=.034). Randomized controlled trials directly comparing REN with pharmacologic management are needed to confirm these pain findings and to compare the effect of REN versus pharmacologic management on other outcomes.

**Nonrandomized Studies**

Numerous nonrandomized, uncontrolled studies have been conducted examining the effectiveness of REN with the Nerivio device for acute migraine.<sup>(16-22)</sup> The most relevant studies are discussed below.

Three single-arm, open-label clinical trials of the Nerivio device were used to inform FDA approval for use in patients other than those with acute migraine due to episodic migraine (Table 6). This includes 2 studies (19,21) in patients with chronic migraine and 1 study (18) in adolescents. In the 2 studies (19,21) of patients with chronic migraine, the mean age was 42 and 44 years, and was 15 years in the study of adolescents.<sup>(18)</sup> In all 3 studies most participants were female (60% to 83%) and of White race (86% to 100%). In the study by Hershey et al (2021)<sup>(18)</sup> 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; study results are summarized in Table 7. 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.

**Table 6. Summary of Key Nonrandomized Clinical Trial Characteristics**

Study	Country	Dates	Participants	Treatment	Follow-Up
Nierenburg et al 2020 <sup>19</sup> .	US, Israel	2019-2020	N=42 adults (18 to 75 years) with ICHD-3 chronic migraine	REN (Nerivio)	24 hours
Grosberg et al 2021 <sup>21</sup> .	US	2019-2020	N=126 adults (18 to 75 years) with ICHD-3 chronic migraine	REN (Nerivio)	24 hours
Hershey et al 2021 <sup>18</sup> .	US	2019-2020	N=45 adolescents (12 to 17 years) with ICHD-3 migraine ≥3 attacks/month	REN (Nerivio)	24 hours

ICHHD: International Classification of Headache Disorders.

**Table 7. Summary of Key Nonrandomized Clinical Trial Results**

Study	Pain Free, 2 hours	Pain Relief, 2 hours	Sustained Pain Free, 24 hours	Sustained Pain Relief, 24 hours	Symptom free, 2 hours	Functional improvement, 2 hours	Return to normal function, 2 hours

<b>Nierenburg et al 2020<sup>19</sup>,</b>	N=38	N=38	N=20	N=32	N=31	N=35	N=35
Proportion (n/N)	26.3% (10/38) <sup>1</sup>	73.7% (28/38) <sup>1</sup>	45.0% (9/20) <sup>1</sup>	84.4% (27/32) <sup>1</sup>	Nausea/vomiting: 58.3% (14/24)	45.7% (16/35)	28.6% (10/35)
					Photophobia: 35.5% (11/31)		
					Phonophobia: 40.0% (10/25)		
<b>Grosberg et al 2021<sup>21</sup>,</b>	N=99	N=99	NR	N=54	N=82	N=40	NR
Proportion (n/N)	19.2% (19/99) <sup>2</sup>	54.5% (54/99) <sup>3</sup>	NR	53.7% (29/54)	Nausea/vomiting: 40.8% (20/49)	47.5% (19/40)	NR
					Photophobia: 36.6% (30/82)		
					Phonophobia: 39.7% (129/73)		
<b>Hershey et al 2021<sup>18</sup>,</b>	N=39	N=39	N=11	N=22	N=31	N=33	NR
Proportion (n/N)	35.9% (14/39) <sup>2</sup>	71.8% (28/39) <sup>3</sup>	90.9% (10/11)	90.9% (20/22)	Nausea/vomiting: 54.5% (12/22)	69.7% (23/33)	NR
					Photophobia: 41.9% (13/31)		
					Phonophobia: 40.0% (10/25)		

NR: not reported.

<sup>1</sup> Pain free and pain relief for at least 50% of treated attacks.

<sup>2</sup> Change in headache severity from mild, moderate, or severe at baseline to none.

<sup>3</sup> Change in headache severity from moderate or severe at baseline to none or mild; or a reduction in headache severity from mild to none.

A post-hoc analysis of the Hershey et al (2021) study, conducted in adolescents, compared the effect of Nerivio use (during the study phase) versus medication use (during the run-in phase) based on within-subject data.(17) Thirty-five adolescents who used medication during the 4-week run-in phase and who had Nerivio use data from the study phase were included in the post-hoc analysis. Nerivio users were more likely to report freedom from pain than medication users (p=.004) but there was no difference between Nerivio and medication in the proportions of patients who achieved pain relief (p=.225). Studies designed to directly compare the Nerivio device with medication are needed to adequately assess comparative effectiveness.

A real-world study (Ailani et al, 2021) sponsored by the Nerivio manufacturer collected data from 23,151 treatments from 5,805 Nerivio users between October 2019 and May 2021.(16) This study is unique in including data on use of the Nerivio device as monotherapy and in combination with medications. Nerivio users reported use of medications (over-the-counter, triptans, or other medications) in addition to the Nerivio device for about one-third of the treatment sessions. For use of Nerivio as monotherapy at 2-hour follow-up, the proportion of patients with freedom from pain, pain relief, return to normal function, and functional disability improvement was 20.3%, 55.6%, 24.9%, and 51.2%, respectively. When the Nerivio device was used in conjunction with medication, proportions ranged from 10.1 to 15.5% for freedom from pain, 38.5 to 51.3% for pain relief, 11.0 to 19.7% for return to normal function, and 39.8 to 49.6% for functional disability improvement, depending on the drug class used. While these results suggest that REN with the Nerivio device is efficacious in a highly selected

group of individuals, additional evidence from well-designed RCTs is needed to thoroughly assess comparative effectiveness.

### **Section Summary: Acute Migraine due to Episodic or Chronic Migraine**

Evidence from 2 small RCTs found REN with the Nerivio device was more effective than a sham device for measures of pain and symptom relief at 2-hours post-treatment. Patients treated with the Nerivio device were also more likely than those treated with a sham device to report 48-hour freedom from pain and pain relief based on 1 RCT. Outcomes related to functional disability and quality of life were not reported. The remaining evidence from post-hoc and nonrandomized studies suggests that REN with the Nerivio device may provide improvements in acute pain and symptomatology. 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) based on test results must be specified in order to adequately evaluate net health benefit.

### **Summary of Evidence**

For individuals with acute migraine due to episodic or chronic migraine who receive REN, the evidence includes 2 RCTs 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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## **Supplemental Information**

### **American Headache Society**

In 2021, the American Headache Society (AHS) issued guidance on the integration of new migraine treatments, including REN, into clinical practice.<sup>(4)</sup> 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 inpatients age 12 to 17 years)
  - Diagnosis of ICHD-3 migraine with aura, migraine without aura, or chronic migraine
  - Either of the following:
    - Contraindications to or inability to tolerate triptans.
    - Inadequate response to 2 or more oral triptans, as determined by EITHER of the following:

- Validated acute treatment patient-reported outcome questionnaire (Migraine Treatment Optimization Questionnaire, Patient Perception of Migraine Questionnaire-Revised, Functional Impairment Scale, Patient Global Impression of Change)
- Clinician attestation.

### **American Academy of Neurology/American Headache Society**

A 2019 joint guideline issued by the American Academy of Neurology and the American Headache Society on the treatment of acute migraine in children and adolescents did not address the use of REN or other nonpharmacologic treatments.(23)

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## **Government Regulations**

### **National:**

There is no national coverage determination.

### **Local:**

There is no local coverage determination.

*(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)*

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## **Related Policies**

Oxygen Therapy for Cluster Headache  
 Sphenopalatine Ganglion Block for Headache  
 Surgical Deactivation of Headache Trigger Sites  
 Transcutaneous Electrical Modulation Pain Reprocessing (Scrambler Therapy)  
 Vagus Nerve Stimulation

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*The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through July 10, 2023, the date the research was completed.*

### Joint BCBSM/BCN Medical Policy History

<b>Policy Effective Date</b>	<b>BCBSM Signature Date</b>	<b>BCN Signature Date</b>	<b>Comments</b>
11/1/22	8/16/22		Joint policy established
11/1/23	8/15/23		Routine maintenance (slp) Vendor Managed: Northwood

Next Review Date: 3<sup>rd</sup> Qtr, 2024

**BLUE CARE NETWORK BENEFIT COVERAGE**  
**POLICY: REMOTE ELECTRICAL NEUROMODULATION FOR MIGRAINES**

**I. Coverage Determination:**

<b>Commercial HMO (includes Self-Funded groups unless otherwise specified)</b>	Not Covered
<b>BCNA (Medicare Advantage)</b>	Refer to the Medicare information under the Government Regulations section of this policy.
<b>BCN65 (Medicare Complementary)</b>	Coinsurance covered if primary Medicare covers the service.

**II. Administrative Guidelines:**

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- Duplicate (back-up) equipment is not a covered benefit.