

## **New Drug Evaluation: Erenumab-aooe injection, subcutaneous**

**Date of Review:** September 2018

**Generic Name:** erenumab-aooe

**End Date of Literature Search:** July 2018

**Brand Name (Manufacturer):** Aimovig™ (Amgen, Inc)

**Dossier Received:** yes

### **Research Questions:**

1. What is the efficacy of erenumab compared to placebo or currently available therapy for preventative treatment of episodic or chronic migraines?
2. Is erenumab safe for the preventative treatment of episodic and chronic migraines?
3. Are there any subgroups (based on age, gender, ethnicity, comorbidities, disease duration or severity) that would particularly benefit or be harmed from treatment with erenumab?

### **Conclusions:**

- There is moderate quality evidence from two phase 3 studies that adult patients with episodic migraine experienced 1 to 2 fewer monthly migraine days with both erenumab 70 mg and 140 mg compared to placebo over 24 weeks [-1.4 (95% confidence interval [CI], -1.9 to -0.9) and -1.9 (95% CI, -2.3 to -1.4), respectively] and with erenumab 70 mg versus placebo over 12 weeks [-1.0 (95% CI, -1.6 to -0.5)].<sup>1,2,3</sup> The clinical significance of this difference is unclear.
- There is moderate quality evidence from one phase 2 study that adult patients with chronic migraines given erenumab 70 mg or 140 mg experienced roughly 2 to 3 fewer monthly migraine days compared to placebo over 12 weeks [-2.5 (95% CI; -3.5 to -1.4) and -2.5 (95% CI; -3.5 to -1.4), respectively].<sup>2,4</sup> The clinical significance of this difference is unclear.
- There is insufficient evidence to evaluate the long term safety of erenumab. The safety population included a total of 2,184 patients. Mortality rates and serious adverse events were similar compared to placebo.<sup>1-4</sup> Adverse events more common with erenumab 70 mg and erenumab 140 mg versus placebo was injection site reaction (6% and 5% versus 3%, respectively) and viral infection (5% and 5% versus 3%, respectively).<sup>1-4</sup>
- There is insufficient evidence to compare the safety and efficacy of erenumab to any other FDA-approved migraine prophylaxis agents in specific subpopulations.<sup>5</sup>

### **Recommendations:**

- Create a new class for calcitonin gene-related peptide (CGRP) antagonists.
- Recommend implementation of prior authorization criteria for CGRP antagonists (**Appendix 2**).

**Background:**

A migraine headache is a debilitating neurovascular brain disorder with a complex pathophysiology and often unpredictable onset.<sup>6</sup> Migraines are the principal cause of neurological disability and one of the most common diseases worldwide.<sup>6</sup> Some migraines are associated with visual or sensory symptoms referred to as an aura.<sup>6</sup> A migraine attack is often characterized by a unilateral, pulsating pain lasting hours to days along with photophobia, vertigo, nausea, and vomiting.<sup>6</sup> Although sensory, visual, speech, or motor aura symptoms may precede a migraine attack, this is not always the case.<sup>6</sup> Episodic migraines are those which occur less than 15 days per month with or without aura.<sup>6</sup> The definition of chronic migraine has recently been updated to include headache (migraine-like or tension-like) occurring on 15 or more days per month for more than 3 months, which, on at least 8 days per month, has migraine headache features.<sup>6</sup> Greater than 10% of the United States population experience migraines with attacks more frequent in adults 18-44 years of age.<sup>7</sup> Women are roughly 3 times more prone to migraines than men.<sup>7,8</sup> Headaches have been identified as one of the major reasons for physician office encounters and account for roughly 3% emergency department (ED) visits.<sup>7</sup> Even with emergency treatment, roughly two-thirds of migraine patients released from the ED experience headache recurrence within 24 hours.<sup>7</sup> Migraines are highly disruptive to quality of life and productivity with the potential for significant impact on patient employment, interpersonal relationships and leisure activities.<sup>9</sup> Dangerous long-term cardiovascular health concerns of migraines include an increased risk for angina, hemorrhagic and ischemic stroke, venous thromboembolism, and myocardial infarction.<sup>10</sup> There are 556 unique Fee-for-Service Oregon Health Plan members who had paid medical claims for a migraine diagnosis between 7/1/17 and 12/31/17.

Migraines may be diagnosed and classified based on presence of aura, frequency of attack, symptoms and severity, as well as location of the pain.<sup>6</sup> The International Headache Society have published 2018 guidelines for the diagnosis of migraine which is summarized in **Table 1**.

**Table 1: Comparison of Migraine without and with Aura<sup>6</sup>**

<b>Migraine without Aura</b>	<b>Migraine with Aura</b>
At least 5 attacks lasting 4–72 hours (when untreated or unsuccessfully treated) fulfilling criteria below:	At least 2 attacks fulfilling criteria below:
Headache has at least two of the following four characteristics: <ol style="list-style-type: none"> <li>1. unilateral location</li> <li>2. pulsating quality</li> <li>3. moderate or severe pain intensity</li> <li>4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)</li> </ol>	At least three of the following six characteristics: <ol style="list-style-type: none"> <li>1. at least one aura symptom spreads gradually over 5 minutes</li> <li>2. two or more aura symptoms occur in succession</li> <li>3. each individual aura symptom lasts 5–60 minutes</li> <li>4. at least one aura symptom is unilateral</li> <li>5. at least one aura symptom is positive</li> <li>6. the aura is accompanied, or followed within 60 minutes, by headache</li> </ol>
During headache at least one of the following: <ol style="list-style-type: none"> <li>1. nausea and/or vomiting</li> <li>2. photophobia and phonophobia</li> </ol>	One or more of the following fully reversible aura symptoms: <ol style="list-style-type: none"> <li>1. visual (fortification spectrum)</li> <li>2. sensory (radiating pin/needle disturbances, numbness)</li> <li>3. speech and/or language</li> <li>4. motor weakness</li> <li>5. brainstem (vertigo, tinnitus, dysarthria, etc; no motor weakness)</li> <li>6. retinal (monocular visual disturbance/scotomata/blindness)</li> </ol>

A migraine attack may be triggered by substances in the diet (alcohol, tyramine- and nitrate-containing foods, monosodium glutamate, etc.), hormonal changes, stress, odors, altered sleep patterns, medication rebound, and weather changes.<sup>11</sup> There is evidence to suggest a genetic origin for the development of migraine headaches, particularly in migraines with aura.<sup>12</sup> Although the etiology of migraine headache is unclear, there are several messenger molecules that may be involved in the transmission of pain signaling including nitric oxide, 5-hydroxytryptamine (5-HT), and calcitonin gene-related peptide (CGRP).<sup>12</sup> CGRP is a 37-amino acid neuropeptide that exists in both the central and peripheral nervous systems as alpha/beta subtypes.<sup>12</sup> Studies have demonstrated that CGRP acts as a potent vasodilator within the intracranial and extracranial vessels and is believed to modulate vascular nociception in the CNS.<sup>12</sup> There are CGRP receptors throughout the cardiovascular and cerebrovascular tissue, kidneys, adrenal glands, and pancreas.<sup>13</sup> Although the role of CGRP in cardiovascular functioning is not well understood, there have been several recent studies which have investigated its effects in migraine pathophysiology and pain transmission.<sup>14,15</sup>

Several therapies approved by the Food and Drug Administration (FDA) are used for chronic migraine prophylaxis. The American Academy of Neurology and American Headache Society recommend that antiepileptic drugs (divalproex sodium/valproic acid, or topiramate) or beta blockers (propranolol, timolol, or metoprolol) be offered to patients for the prevention of episodic migraine (Level A: established efficacy based on 2 or more high quality trials).<sup>16</sup> The AAN also established onabotulinumtoxinA as an effective treatment option for patients with chronic migraine to decrease the number and severity of headaches (Level A) and as probably effective for improvement of health-related quality of life (Level B: probably effective based on 1 high quality or 2 moderate quality studies).<sup>16</sup> The AAN does not consider onabotulinumtoxinA to be effective for episodic migraine and recommends against its use in that patient population (Level A: ineffective based on at least 1 high quality or 2 moderate quality studies).<sup>16</sup> There are numerous preventative migraine therapies options that have been used successfully and more are currently under development.<sup>17</sup> A list of commonly prescribed FDA-approved treatments for migraine prophylaxis, their doses, and key safety information is provided in **Table 2**.

**Table 2. Selected FDA-Approved Treatments for Migraine Prophylaxis (Modified table)<sup>5</sup>**

Product Name	Dosing/Administration	Efficacy	Safety and Tolerability Concerns	Comments
Propranolol	20-80mg TID-QID	Treatment effect not in the label	Anaphylaxis, bradycardia	Bronchospasm and hypoglycemia in applicable populations
Timolol	10-15mg BID	Treatment effect not in the label	Anaphylaxis, bradycardia	Bronchospasm and hypoglycemia in applicable populations
Divalproex/sodium valproate	250-500mg BID	Treatment effect: 1.5 to 2.2-day reduction in monthly migraine days	Boxed warning for hepatotoxicity	Fetal risk of neural tube defects
Topiramate	50mg BID	Treatment effect: 1.0 to 1.3-day reduction in monthly migraine days	Paresthesias, weight loss	Fetal risk of cleft lip and palate
OnabotulinumtoxinA	Total dose 155 units divided across 7 muscles; administered every 12 weeks	Treatment effect: 1.4 to 2.3-day reduction in monthly headache days from baseline	Transient weakness may occur in muscles that are injected	Approved for chronic migraine only; administered intramuscularly by a physician

Abbreviations: BID = twice daily; TID = three times daily; QID – four times daily

One of the most important primary outcome measures used to evaluate effectiveness of migraine therapy is acute pain resolution.<sup>18,19</sup> However, there have also been several clinical tools used to document impact of migraine on patient disability and health-related quality of life. The Migraine Disability Assessment (MIDAS) is a five item questionnaire that was created to help patients track the number of days in the previous three months that a headache affected their

ability to carry out daily tasks.<sup>20</sup> No minimal clinically important difference (MCID) has been established for MIDAS. The Headache Impact Test (HIT-6) is a 6-question tool similar to MIDAS but each response is given an individual score and then tallied to assess overall impact.<sup>20</sup> The HIT-6 ranges from 36 to 78 points with higher scores indicative of greater impact.<sup>20</sup> A score of 60 or more on the HIT-6 is indicative that the migraine causes severe disability.<sup>20</sup> However, no clear MCID has been established for the HIT-6. The Migraine-Specific Quality of Life Questionnaire (MSQ) is a 14-item questionnaire which examines the extent of migraine impact on the patient's daily social and work-related activities, as well as their emotions.<sup>20</sup> The MSQ ranges from 0 to 100 with higher scores suggestive of a better quality of life.<sup>20</sup> A MCID for each of the MSQ domains established by previous trials has been reported to be -10.9 (role function-restrictive), -8.3 (role function-preventative), and -12.2 (emotional function).<sup>20</sup>

The migraine physical function impact diary (MPFID) is a self-administered, 13-item instrument designed to assess how the patient's migraine affects everyday activities and the impact on physical impairment.<sup>5,20</sup> Patient responses are based on the previous 24 hours and scored on a 5-point scale (range 1 to 5, 5 = more negative impact).<sup>5,20</sup> Each MPFID domain score is converted and scaled to 100 points.<sup>5,20</sup> The scores for the 28-day period are the averaged and recorded.<sup>5,20</sup> The MPFID instrument has not been validated nor has a minimal clinically important change been identified.<sup>5</sup>

See **Appendix 1 for Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

#### **Clinical Efficacy:**

Erenumab is a calcitonin gene-related peptide receptor antagonist indicated for the preventative treatment of migraine in adults. Erenumab was approved based on 3 studies (two phase 3 RCT and one phase 2 RCT) in patients with episodic or chronic migraine (**Table 5**). The primary outcome in the trials was mean monthly migraine days compared to baseline.<sup>2</sup> Erenumab therapy demonstrated reductions in monthly migraine days in all 3 trials versus placebo.<sup>2</sup>

In the first phase 3 trial (STRIVE; study 296; n=955), erenumab treatment was compared to placebo in the treatment of episodic migraine.<sup>1,2,5</sup> Baseline demographics, inclusion criteria, and exclusion criteria are reported in Table 5.<sup>1,2,5</sup> After a 4-week baseline period, patients were randomized 1:1:1 and entered into a 24-week double-blind active treatment phase to receive placebo, erenumab 70 mg, or erenumab 14 mg with a 12-week follow up.<sup>1,2,5</sup> The primary outcome studied was the change in mean number of monthly migraine days from baseline to the last 3 months of the double-blinded treatment period.<sup>1,2,5</sup> A key secondary endpoint was achievement of at least a 50% reduction from baseline in mean monthly migraine days. Additional secondary endpoints included changes from baseline in MPFID scores.<sup>1,2,5</sup> Patients used electronic health diaries to complete the MPFID for physical function and everyday activities and to record details about their migraine symptoms, pain severity, medication use, date and time of headaches.<sup>1,2,5</sup> A statistically significant mean reduction in monthly migraine days was observed in erenumab 70 mg and 140 mg versus placebo from baseline to the last 3 months of treatment.<sup>1,2,5</sup> The least squares mean difference (LSM) for erenumab 70 mg versus placebo was -1.4 (95% CI -1.9 to -0.9; p<0.001) and the LSM for erenumab 140 mg versus placebo was -1.9 (95% CI 2.3 to -1.4; p<0.001).<sup>1,2,5</sup> The key secondary endpoint of proportion of subjects with at least a 50% reduction in mean monthly migraine days from baseline to the last 3 months of treatment was higher in erenumab 70 mg and 140 mg versus placebo (43.3%, 50.0%, and 26.6% respectively; p<0.001; NNT=6 and 5).<sup>1,2,5</sup>

The second phase 3 trial (ARISE; study 297; n=577) had similar inclusion criteria, exclusion criteria, primary and secondary outcomes as the STRIVE trial.<sup>2,3,5</sup> However, patients only received erenumab 70 mg or placebo monthly for 12 weeks, followed by a 28-week open-label treatment phase of erenumab 70 mg monthly.<sup>2,3,5</sup> Changes from baseline in HIT-6, MIDAS, and MSQ scores were additional exploratory endpoints.<sup>2,3,5</sup> The LSM change in MMDs favored erenumab over placebo (-2.9 vs. -1.8, respectively) with a LSM difference of -1.0 (95% CI -1.6 to -0.5, p<0.001) days.<sup>2,3,5</sup> A higher proportion of erenumab patients achieved

a 50% or greater reduction in MMDs compared to placebo (39.7% vs. 29.5%, respectively) with an adjusted odds ratio (OR) of 1.6 (95% CI 1.1 to 2.3, p = 0.010).<sup>2,3,5</sup> Other secondary patient-reported outcomes of potential relevance were not statistically significant.<sup>2,3,5</sup>

Study 295 (n=667) was a phase 2 RCT in chronic migraine patients.<sup>3,4,5</sup> Patients were randomized 3:2:2 to placebo, edaravone 70 mg, and edaravone 140 mg.<sup>3,4,5</sup> Patient demographics and outcomes were similar to STRIVE and ARISE with a baseline MMD of 18 days among all groups.<sup>3,4,5</sup> A statistically significant greater mean MMD reduction was noted for both erenumab treatment doses versus placebo with a LSM difference of -2.46 (95% CI -3.52 to -1.39; p< 0.001) for erenumab 70 mg versus placebo and -2.45 (95% CI -3.52 to -1.38; p<0.001) for erenumab 140 mg versus placebo.<sup>3,4,5</sup> The proportion of subjects with a 50% or greater reduction in MMD from baseline to the last 4 weeks of the treatment phase was 23.5%, 39.9% (NNT=7), and 41.2% (NNT=6) for placebo, erenumab 70 mg and erenumab 140 mg, respectively (p<0.001 for both erenumab doses).<sup>3,4,5</sup>

### *Limitations*

Limitations to this evidence include an inability to detect effects in the male population given the low percentage of male participants. Physical function and ability to perform daily activities was measured with the MPFID tool which has not been widely recognized as a validated form of assessment. There may be little value in statistically significant MPFID results without an established minimal clinically important difference value.

A migraine day could be counted if a patient took an acute migraine-specific drug to treat a headache regardless of headache duration or pain symptoms. Given the subjective nature of the definition of a migraine day, the clinical significance of 1 to 2 fewer migraine days per month is uncertain. The 50% responder rate was based on monthly migraine reduction compared to baseline, but the baseline monthly migraine days were initially relatively low which indicates a population with mild disease. Therefore, it is unclear whether or not erenumab would be effective in moderate to severe disease. Only study 295 evaluated the use of erenumab in treating chronic migraine.

Many oral agents are FDA-approved for chronic migraine therapy but patient adherence has typically been poor. Treatment effects in patients who failed more than 2 migraine preventative medications are unknown due to their exclusion from trials. Erenumab is given subcutaneously which is may be a less preferred route of administration compared to oral agents for many patients. The primary authors for phase 3 studies are also creators of the IHS guidelines with multiple grants, consultancy and industry support from major pharmaceutical manufacturers including, but not limited to, Amgen. Head-to-head studies may be needed to evaluate erenumab's place in therapy.

### **Clinical Safety:**

Side effects observed in clinical trials which were more common with erenumab than placebo include infection from any cause, injection site reaction, viral infection, constipation, and cramps/muscle spasms (**Table 3**).<sup>2,5</sup> No serious adverse reactions occurred in more than 1% of patients or more frequently than placebo.<sup>2,5</sup> Overall discontinuations due to adverse reactions was low in clinical trials (1.2, 1.7, and 2.4% for placebo, erenumab 70 mg, and erenumab 140 mg, respectively).<sup>2,5</sup>

**Table 3: Adverse Drug Reactions Which Occurred  $\geq 2\%$  More Commonly in Erenumab--Treated Patients than Placebo-Treated Patients<sup>2</sup>**

Adverse Reactions	Placebo (n=890) N	Erenumab 70 mg (n=787) N	Erenumab 140 mg (n=507) N
Infection, all	25%	25%	27%
Injection site reaction	3%	6%	5%
Infection, viral	3%	5%	5%
Constipation	1%	1%	4%
Cramps, muscle spasms	0%	0%	2%

Theoretical concerns of impaired vasodilation from CGRP inhibition include worsening ischemia in patients with angina, increased thrombotic events in at-risk individuals, and a worsening of Raynaud's phenomenon symptoms.<sup>5</sup> Patients over age 65 with higher cardiovascular risk and those with existing cardiovascular disease were not recruited in the clinical trials.<sup>5</sup> The FDA concluded that nonclinical data did not raise substantial concern about cardiovascular risk, and therefore, no post-market safety studies were required for erenumab.<sup>5</sup> Safety of erenumab in pregnancy and breastfeeding mothers as well as long-term risks of CGRP blockade beyond 24 weeks remain unknown.<sup>5</sup>

**Comparative Endpoints:**

Clinically Meaningful Endpoints:

- 1) Migraine frequency
- 2) Migraine intensity
- 3) Migraine duration
- 4) Serious adverse events
- 5) Study withdrawal due to an adverse event

Primary Study Endpoint:

- 1) Change from baseline in migraine days per month

**Table 4: Pharmacology and Pharmacokinetic Properties.<sup>2,5,21</sup>**

Parameter	
Mechanism of Action	A human monoclonal antibody that binds to the CGRP receptor and antagonizes CGRP receptor function
Bioavailability	Subcutaneous: 82%
Distribution and Protein Binding	3.86 L
Elimination	Degradation by reticuloendothelial cells and breakdown within lysosomes of cells with the CGRP receptor
Half-Life	28 days
Metabolism	Catabolism into amino acids

Abbreviations: CGRP = calcitonin gene-related peptide; L = liter

**Table 5. Comparative Evidence Table.**

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/ NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Goadsby, et al (Study 296 - STRIVE) <sup>1,2,5</sup>  Phase 3 RCT, MC, DB, PC, PG study of patients with EM	1. Placebo  2. Erenumab 70 mg  3. Erenumab 140 mg  Given SQ once every 4 weeks x24 weeks	<u>Demographics:</u> - Mean Age: 41 (range: 18-65) - Age <56: 89% - Female: 85%  - Geographic region North America: 50% - Race: White: 89% Black: 7% Other: 4% - BMI: 27+/-6 kg/m <sup>2</sup> - Disease duration: 20 years - Mean migraine days per month: 8.3  <u>Key Inclusion Criteria:</u> - History of migraine for ≥12 months - Migraine frequency of 4 to 14 days/month with <15 headache days/month  <u>Key Exclusion Criteria:</u> - Older than 50 years old at migraine onset; - Hx of cluster HA or hemiplegic migraine - No therapeutic response to more than 2 preventive tx categories; - Recent use of ergots or triptans, simple analgesics, or opioid or butalbital-containing analgesics - Recent use of migraine preventive medications or prior use botulinum	<u>ITT:</u> 1. 319 2. 317 3. 319  <u>PP:</u> 1. 316 2. 312 3. 318  <u>Attrition:</u> 1. 3 (1%) 2. 5 (2%) 3. 1 (<1%)	<u>Primary Endpoint:</u> Change from baseline in migraine days per month 1. -1.8 2. -3.2 3. -3.7 1 vs. 2: LSMD -1.4 (95% CI, -1.9 to -0.9); p <0.001 1 vs. 3: LSMD -1.9 (95% CI, -2.3 to -1.4); p <0.001  <u>Key Secondary Endpoints:</u> Proportion with ≥ 50% reduction in monthly migraine days 1. 26.6% 2. 43.3% 3. 50.0%  1 vs. 2. OR 2.1 (95% CI, 1.5 to 3.0); p-value <0.001 1 vs. 3. OR 2.8 (95% CI, 2.0 to 3.9); p-value <0.01  Change from Baseline in Mean Monthly Average Impact on Everyday Activities Score (MPFID) – Adjusted FDA analysis 1. -3.3 2. -5.5 3. -5.9 1 vs. 2. LSMD -2.2 (95% CI, -3.3 to -1.2); p<0.001 1 vs. 3. LSMD -2.6 (95% CI, -3.6 to -1.5); p<0.001  Change from Baseline in Mean Monthly Average MPFID Physical Impairment Domain Scores – Adjusted FDA analysis 1. -2.4	NA  NA  16.7%/6  23.4%/5  NA  NA  NA	<u>Outcome:</u> Overall percent of patients reporting at least 1 adverse event: 1. 63% 2. 57% 3. 56%  SAEs 1. 7 (2%) 2. 8 (3%) 3. 6 (2%)  Discontinuation from Adverse Events 1. 8 (3%) 2. 7 (2%) 3. 7 (2%)	NA for all	<b>Risk of Bias (low/high/unclear):</b> <u>Selection Bias:</u> Low. Subjects given ID numbers with drug allocation centrally determined by Interactive Response Technology; patients, site personnel, trial sponsors blinded to treatment assignments <u>Performance Bias:</u> Unclear. Subjects and investigators blinded but no details provided <u>Detection Bias:</u> Unclear. Subjective patient-reported outcomes collected, tallied, and converted by unmentioned parties <u>Attrition Bias:</u> Low. Full analysis in final protocol included all patients who underwent randomization <u>Reporting Bias:</u> High. Patients completed diary entries over prior 24 hours with no safeguards against information gaps or overlap; original protocol collected PROs in eDiary for secondary endpoints (MIDAS, MSQ, HIT-6, etc) were omitted from the published draft due to non-significant results of study 297 (FDA allowed change); MPFID scores transformed into 100 point scale without methodology disclosed <u>Other Bias:</u> Unclear. Main author an IHS Committee member who was also an author for the 2018 <i>Guidelines for controlled trials of preventive treatment of chronic migraine in adults</i> published after the study  <b>Applicability:</b> <u>Patient:</u> Excluded patients over age 65 and with CVD; Effects of CGRP receptor blockade in CVD patients with ischemia unknown could theoretically interfere with cardioprotective vasodilatory mechanisms that occur during acute ischemia; females were likely over-represented in a ratio of 6:1; percentage of blacks and Hispanics lower than expected; no concurrent migraine prophylactic medication allowed <u>Intervention:</u> Appropriate FDA-approved dose; subcutaneous administration



								<b>Outcomes:</b> Migraine day definition (mean monthly change and proportion of subjects with ≥ 50% reduction) as endpoints subject to wide variation and interpretation; migraine duration of 30 minutes or greater included in the calculation of the primary endpoint; MPFID not validated <b>Setting:</b> 69 centers in Denmark, France, Greece, Portugal, Russian Federation, Spain, Switzerland, and the U.S.
3. Tepper, et al (Study 295) <sup>2,4,5</sup>  Phase 2, randomized, DB, PC study of CM patients	1. placebo  2. erenumab 70 mg  3. erenumab 140 mg  Dosed SQ every 4 weeks x12weeks	<b>Demographics:</b> -Mean Age: 42 -Female: 83% -Geographic region: North America: 47% -White: 94% -BMI: 26 -Disease duration: 21 years -Migraine days per month: 18  <b>Key Inclusion Criteria:</b> - Hx of 15 or more HA days/month, with 8 or more migraine days/month  <b>Key Exclusion Criteria:</b> - Chronic migraine where the patient was not experiencing any pain free periods - Opioid use for >12 days during three months prior to screening - Butalbital use >6 days during the 3 months prior - No therapeutic response in prophylaxis of migraine after an adequate trial of > 3 prophylactic medications - Use of a prohibited migraine prophylactic medication within two months prior	<b>ITT:</b> 1. 286 2. 191 3. 190  <b>PP:</b> 1. 281 2. 188 3. 187  <b>Attrition:</b> 1. 5 (2%) 2. 3 (2%) 3. 3 (2%)	<b>Primary Endpoint:</b> Change from baseline in migraine days per month 1. -4.2 2. -6.6 3. -6.6  1 vs. 2: LSMD -2.5 (95% CI; -3.5 to -1.4); p-value <0.001 1 vs. 3: LSMD -2.5 (95% CI; -3.5 to -1.4); p-value <0.001  <b>Key Secondary Endpoints:</b> Proportion of patients with ≥50% reduction in monthly migraine days from baseline 1. 23.5% 2. 39.9% 3. 41.2%  Adjusted odds ratio: 1 vs. 2: 2.2 (95% CI; 1.5 to 3.3) p-value <0.001 1 vs. 3: 2.3 (95% CI; 1.6 to 3.5) p-value <0.001	NA  NA  16.4%/7  17.7%/6	<b>Outcome:</b>  Overall percent of patients reporting at least 1 adverse event  1. 39% 2. 44% 3. 47%  Overall adverse events leading to treatment discontinuation:  1. 1% 2. 0% 3. 1%	NA for all	<b>Risk of Bias (low/high/unclear):</b> <b>Selection Bias:</b> Low. Sponsor-generated randomization sequence executed by IVR; patients, sponsor, and study personnel all masked to treatment assignment; baseline characteristics similar among groups <b>Performance Bias:</b> Low. Placebo and active drug presented in identical vials, storage containers, etc <b>Detection Bias:</b> Low. Analysis included all patients randomized to their respective treatment categories <b>Attrition Bias:</b> Low. Minimal dropouts; missing data unlikely to influence results <b>Reporting Bias:</b> Unclear. Electronic diaries used to record migraine incidence, severity, and symptoms migraine; if at least 14 days of 28-day interval was recorded in e-diary, then the monthly measurement was prorated to 28-day or computed as average from the available observed days of data <b>Other Bias:</b> High. One of main authors also on IHS Committee who created <i>2018 Guidelines for controlled trials of preventive treatment of chronic migraine in adults</i> ; study sponsor developed study protocol with investigators and also managed study sites, performed the statistical analysis, and funded support of medical writers  <b>Applicability:</b> <b>Patient:</b> Excluded patients taking concurrent migraine prophylaxis medications; patients with diagnosis of chronic migraine due to medication overuse of triptans, ergots, and other analgesics were also excluded <b>Intervention:</b> Both FDA-approved doses of erenumab studied; subcutaneous administration

		- Patients with diagnosis or history of pertinent select comorbid neurologic or mental health conditions, cardiovascular issues, or substance abuse - Body mass index >40 kg/m <sup>2</sup>						<p><u>Comparator</u>: Placebo control appropriate to establish safety and efficacy</p> <p><u>Outcomes</u>: Primary endpoint was measured in the last four weeks of the double-blind treatment period-</p> <p><u>Setting</u>: 69 centers in North America (US and Canada) and Europe (Czech Republic, Denmark, Germany, Finland, Norway, Poland, Sweden, and United Kingdom).</p>
<p><u>Abbreviations</u>: ARR = absolute risk reduction; CAB = Coronary Artery Bypass; CI = confidence interval; CM = chronic migraine; CVD = cardiovascular disease; EM = episodic migraine; HA = headache; HIT-6 = Headache Impact Test; Hx = history; IHS = International Headache Society; ITT = intention to treat; IVR = interactive voice response; LSMD = least squares mean difference; mITT = modified intention to treat; MI = myocardial infarction; MIDAS = Migraine Disability Assessment; MPFID= migraine physical function impact dairy; MSQ = Migraine-Specific Quality of Life Questionnaire; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OR = odds ratio; PP = per protocol; PG = parallel group; PROs = patient-reported outcomes; TIA = transient ischemic attack; SAE = serious adverse events; SQ = subcutaneously; Tx = treatment</p>								

## References:

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## Appendix 1: Prescribing Information Highlights

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use AIMOVIG safely and effectively. See full prescribing information for AIMOVIG.

**AIMOVIG™ (erenumab-aooe) injection, for subcutaneous use**  
**Initial U.S. Approval: 2018**

#### INDICATIONS AND USAGE

AIMOVIG is a calcitonin gene-related peptide receptor antagonist indicated for the preventive treatment of migraine in adults (1)

#### DOSAGE AND ADMINISTRATION

- For subcutaneous use only (2.1, 2.2)
- Recommended dosage is 70 mg once monthly; some patients may benefit from a dosage of 140 mg once monthly (2.1)
- The 140 mg dose is administered once monthly as two consecutive injections of 70 mg each (2.1)
- The needle shield within the white cap of the prefilled autoinjector and the gray needle cap of the prefilled syringe contain dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex (2.2)
- Administer in the abdomen, thigh, or upper arm subcutaneously (2.2)

- See Dosage and Administration for important administration instructions (2.2)

#### DOSAGE FORMS AND STRENGTHS

- Injection: 70 mg/mL solution in a single-dose prefilled SureClick® autoinjector (3)
- Injection: 70 mg/mL solution in a single-dose prefilled syringe (3)

#### CONTRAINDICATIONS

None (4)

#### ADVERSE REACTIONS

The most common adverse reactions in AIMOVIG clinical studies (occurring in at least 3% of treated patients and more often than placebo) are injection site reactions and constipation (6.1)

**To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-77-AMGEN (1-800-772-6436) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).**

**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Patient Labeling.**

**Revised: 5/2018**

## Calcitonin Gene-Related Peptide (CGRP) antagonists

### Goal(s):

- Promote safe use of CGRP inhibitors in adult patients
- Promote use that is consistent with medical evidence and product labeling

### Length of Authorization:

- Initial: Up to 3 months
- Renewal: Up to 12 months

### Requires PA:

- All calcitonin gene-related peptide (CGRP) antagonists

### Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA-approved indication?	<b>Yes:</b> Go to #3	<b>No:</b> Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	<b>Yes:</b> Go to #4	<b>No:</b> Pass to RPh. Deny; not funded by the OHP.
4. Is this a request for renewal of a previously approved Fee-For-Service prior authorization of a CGRP antagonist for management of migraine headache?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #5

Approval Criteria		
5. Is there documentation that the patient has experienced 4 or more migraine days in the previous month?	<b>Yes:</b> Document migraine days per month _____ Go to #6	<b>No:</b> Pass to RPh. Deny; medical appropriateness
6. Do chart notes indicate headaches are due to medication overuse?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #7
7. Has the patient failed an adequate trial ( $\geq 6$ weeks with a documented adherence of $\geq 80\%$ ) of an FDA-approved migraine prophylaxis medication from each of the following classes: beta-blockers, anticonvulsants, and tricyclic antidepressants?  OR  Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to each of the above migraine prophylaxis classes?	<b>Yes:</b> Document agents used and dates _____ _____  Go to #8	<b>No:</b> Pass to RPh. Deny; medical appropriateness
8. Has the patient received an injection with botulinum toxin for headache treatment once in the previous 2 months?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness	<b>No:</b> Go to #9
9. Is the medication being prescribed by or in consultation with a neurologist or headache specialist?	<b>Yes:</b> Approve for 3 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Do chart notes indicate headaches are due to medication overuse?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #2

2. Has the patient experienced a documented positive response to therapy, as demonstrated by a reduction in migraine headache frequency and/or intensity from baseline?	<b>Yes:</b> Document response Approve for 12 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness
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*P&T/DUR Review: 9/2018 (DE)  
Implementation: TBD*