



L. S. SKAGGS PHARMACY INSTITUTE

**UTAH MEDICAID DUR REPORT**

**MONOCLONAL ANTIBODIES  
FOR  
MIGRAINE PREVENTION**

Erenumab-aooe (Aimovig)

Fremanezumab-vfrm (Ajovy)

Galcanezumab-gnlm (Emgality)

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## Introduction

Migraine headache is a common neurological condition impacting about 18% of women and 7% of men and varies among patients with respect to frequency, intensity, duration, and the extent of disability experienced.<sup>1,2</sup> Migraine pharmacotherapy includes acute and preventive medications. Preventive treatment is generally offered to patients when migraine attacks have “...substantial impact on their lives and have not responded to acute care, or where the frequency of migraine attacks is such that the reliance on acute care medications would increase the potential for drug-induced (rebound) headache.”<sup>1</sup>

A new therapeutic class of migraine-preventive therapies came to market in 2018: the calcitonin gene-related peptide (CGRP) antagonists. These are monoclonal antibodies that antagonize CGRP by binding either to the CGRP receptor (as with erenumab) or binding to CGRP ligand (as with galcanezumab and fremanezumab). CGRP antagonists are indicated for migraine prevention in adult patients with episodic or chronic migraine and are administered less frequently than daily-dosed oral options for migraine prevention. The purpose of this report is to review the appropriate use of the newly approved monoclonal antibodies and factors that may influence efficacy and safety outcomes.

These monoclonal antibodies were reviewed by the Pharmacy and Therapeutics Committee in November of this year, along with other FDA-approved agents for migraine prevention: divalproex, topiramate, propranolol, timolol, and onabotulinumtoxinA. Currently, there are no prior authorization requirements for the CGRP antagonists. Prior-authorization criteria are in place for botulinum toxins. Patients can apply to receive onabotulinumtoxinA for chronic migraine prevention or for its other FDA-approved indications.

## Methodology

Information regarding the pivotal controlled trials for the CGRP antagonists was obtained from the prescribing information (ie package inserts) and US Food and Drug Administration (FDA) Summary Reviews from the drug approval packages that are maintained on the FDA website (Drugs@FDA). ClinicalTrials.gov was searched, using drug terms, to identify completed study information. Additionally, the full-text for clinical trials were found by searching OvidMedline and Embase using the drug names as keywords. The following websites were searched, for guidelines pertaining to the prevention of migraine:

- American Academy of Neurology (AAN); [www.aan.com](http://www.aan.com)
- The National Institute for Health and Care Excellence (NICE); <https://www.nice.org.uk/>
- Canadian Headache Society (CHS); <https://headachesociety.ca/guidelines/>

Relevant information from the *Utah Medicaid Pharmacy and Therapeutics Committee Drug Class Review: FDA-Approved Agents for Migraine Prophylaxis* report, dated November 2018 and prepared by the University of Utah’s Drug Regimen Review Center, was incorporated into this document. Additional search information is provided in **Appendix A**.

## Disease Overview

Data from a 2012 national survey found that about 14% of US adults experienced migraine or severe headache during the 3-month recall period.<sup>3</sup> Migraine prevalence is higher among women (11% to 16%) compared to men (5% to 8%).<sup>4</sup> In the pediatric population, prevalence increases with increasing age.<sup>5</sup> Eight percent to 23% of adolescents 15 years or older experience migraine. Younger patients also experience migraine, however, at a lower prevalence (3% for ages 3 to 7 years, and 4% to 11% for ages 7 to 11 years).<sup>5</sup>

Migraine symptoms can reduce quality of life and negatively affect engagement or productivity at school, work, or in social settings.<sup>2,4</sup> Most patients rate their migraine-related pain as severe.<sup>3,4</sup> Approximately 20% of patients with episodic migraine suffer from moderate to severe headache-related disability.<sup>6</sup> Of the subpopulation experiencing high-frequency migraines (ie, chronic migraine), approximately 50% have moderate to severe headache-related disability.<sup>6</sup>

Migraine is classified according to symptomatology (migraine with or without aura) and frequency (episodic or chronic migraine). The diagnosis and classification of migraine has been delineated in the International Classification of Headache Disorders-3 (ICHD-3), developed by the International Headache Society.<sup>7</sup> Migraine without aura usually presents unilaterally with pulsating moderate to severe pain that can be aggravated by physical exertion. Patients may experience nausea, photophobia, or phonophobia. Migraine without aura can last 4 to 72 hours (2 to 72 hours in children). Migraine with aura is characterized by reversible neurological symptoms of the brainstem that usually precede the migraine, but may also occur during the episode. Aura symptoms include any of the following: dysarthria, vertigo, tinnitus, impaired hearing, diplopia, or ataxia. Hemiplegic type aura involves motor weakness, and other reversible visual, sensory or speech dysfunction presentations.

Patients who experience headache (migraine- or tension-like) occurring  $\geq 15$  days per month for at least 3 months, with at least 8 days/month involving features of migraine headache, are classified as having chronic migraine. Chronic migraine (CM) accounts for about 8% of the total migraine cases.<sup>6,7</sup> Episodic migraine (EM) generally refers to migraine occurring less than 15 days per month; an explicit definition for EM is not stated in ICHD-3. Median monthly headache-days reported for the population with EM generally range from about 2 to 3, and 20 to 22 for patients with CM.<sup>8</sup> Frequent use of acute medications can increase headache episodes (ie, medication-overuse headache). Medication-overuse headache has been defined as headache occurring  $\geq 15$  days per month that has worsened during acute-medication overuse; acute-medication overuse is defined as the use of (a) ergotamine, triptans, opioids or combination analgesic medications for  $\geq 10$  days/month for  $> 3$  months, or (b) simple analgesics or any combination of ergotamine, triptans, analgesics or opioids on  $\geq 15$  days/month for  $> 3$  months.<sup>9</sup>

## Pharmacotherapy for Migraine Prevention

Aside from the CGRP antagonists, other FDA-approved products indicated for migraine prevention include the anticonvulsants, divalproex and topiramate, the beta blockers, timolol and propranolol, and the neuromuscular blocker, onabotulinumtoxinA. Table 1 of **Appendix B** provides indication and formulation information for these additional FDA-approved migraine-preventive products. There are various off-label medications (ie, medications without an FDA approval for migraine prevention) that also have supportive evidence for their use, as described in Table 1.

The oral agents (divalproex, topiramate, timolol, and propranolol) were approved for migraine prevention prior to the clinical diagnostic distinction between chronic and episodic migraine (introduced in 2004 by the International Headache Society); the approvals were based on studies of primarily patients with episodic migraine.<sup>10</sup> The oral agents are administered on a daily basis. OnabotulinumtoxinA (Botox), was the first medication to gain approval for the subpopulation with chronic migraine; however, it was not effective for episodic migraine prevention. OnabotulinumtoxinA is administered intramuscularly, across head and neck muscles, once every 12 weeks. The newly approved CGRP antagonists are administered subcutaneously, once monthly (all CGRP antagonists) or once quarterly (fremanezumab only) and their efficacy was demonstrated for both episodic and chronic migraine prevention.

Guidelines for the management of migraine predate approvals for the CGRP antagonists. The most recent 2012 American Academy of Neurology and the American Headache Society (AAN/AHS) guideline for long-term prevention of episodic migraine in adults classifies therapies based on the level of evidence supporting their use.<sup>11</sup> Medications with established efficacy supported by the highest-quality evidence include divalproex, sodium valproate, topiramate, metoprolol, timolol, and propranolol. Agents that are “probably effective” include amitriptyline, venlafaxine, atenolol, and nadolol. Medications that are “possibly effective,” with less certainty than the previous groups, include lisinopril, candesartan, clonidine, guanfacine, carbamazepine, nebivolol, pindolol, and cyproheptadine. Authors highlight that treatment selection depends on patient co-morbidities and tolerability, as many of these medications have other pharmacological effects and indications.<sup>11</sup> Preventive agents recommended among clinical guidelines for migraine prevention, including those published by the ANN/AHS, the National Institute for Health and the Care Excellence, and the Canadian Health Society, are summarized in Table 1.

Regarding chronic migraine, guidelines have not been developed specifically for this subpopulation. Thus, in 2015, neurologist experts (Amaal Starling, MD, and David Dodick, MD) of the Mayo Clinic developed an evidence-based “best-practices” guide.<sup>12</sup> In addition, the AAN has provided a 2016 guideline focusing on appropriate uses of botulinum toxins.<sup>13</sup> In the 2015 best-practice guide, authors explained that both onabotulinumtoxinA (OBTA) and topiramate have been shown to be efficacious in randomized, placebo-controlled trials of patients with chronic migraine.<sup>12,14,15</sup> The 2016 AAN guideline on the use of OBTA recommends offering OBTA

to patients with CM to reduce the number of headache days and improve health-related quality of life.<sup>13</sup> Authors also concluded that there is insufficient evidence comparing OBTA to topiramate for chronic migraine.<sup>13</sup>

## **Pediatric Treatment**

Topiramate is the only FDA-approved medication for migraine prophylaxis in the pediatric population (for adolescents 12 years and older). Guidelines for the treatment of migraine in the pediatric population by the American Academy of Neurology were last published in 2004 and are currently being updated. In 2004, authors found insufficient evidence to support or refute the use of amitriptyline, divalproex sodium, topiramate, or levetiracetam for migraine prevention.<sup>5</sup> Evidence at that time was conflicting for preventive therapy with propranolol or trazodone.<sup>5</sup>

More recently, authors of a 2015 systematic review concluded that there is limited evidence to support the use of beta-blockers in pediatric patients.<sup>16</sup> However, provided that propranolol has a good safety profile in patients without respiratory or cardiovascular co-morbidities, it may be reasonable to try, with the understanding that only some patients will have an adequate response. Topiramate is potentially beneficial compared to placebo, though evidence is limited, and that the difference in the treatment effect between topiramate and propranolol is unclear.<sup>16,17</sup>

The National Institute for Health and Care Excellence (NICE) provides a guideline for migraine prevention in pediatric patients over 12 years old, last updated in 2015. The committee recommends offering topiramate, propranolol, or amitriptyline based on the patient's preference, comorbidities, and the risk of adverse events.<sup>18</sup>

## **When to Initiate Therapy**

Information regarding when to initiate preventive treatment is discussed in a few guidelines:

- The 2012 Canadian Headache Society (CHS) guideline for the management of episodic migraine contains the following consensus recommendations:
  - Consider prophylactic therapy "...in patients whose migraine attacks have a significant impact on their lives despite appropriate use of acute medications and trigger management / lifestyle modification strategies."<sup>19</sup>
  - Prophylactic therapy should be considered if a patient must use acute medications so frequently to mitigate migraine attacks such that they are placed at risk of medication-overuse headache. The CHS defines acute-medication overuse as, "...use of opioids, combination analgesics, or triptans on ten days a month or more, or use of simple analgesics (acetaminophen, ASA, NSAIDs) on 15 days a month or more,"<sup>19</sup> and stated, "[b]ased on current evidence, it would appear most advantageous for patients with

migraine and medication overuse to both stop their medication overuse and at the same time to start a prophylactic medication.”<sup>19</sup>

- Consider prophylactic therapy for patients with “...greater than three moderate or severe headache days a month when acute medications are not reliably effective, and for patients with greater than eight headache days a month even when acute medications are optimally effective because of the risk of medication overuse headache.” Authors highlighted that other situations involving less frequent migraine days per month may also be considered for prophylactic therapy (eg, hemiplegic migraine or for patients with contraindications to acute migraine therapies).<sup>19</sup>
- An older guideline published in 2000 by the AAN advises that preventive therapy should be considered “... for those patients whose migraine has a substantial impact on their lives and have not responded to acute care, or where the frequency of migraine attacks is such that the reliance on acute care medications would increase the potential for drug-induced (rebound) headache.”<sup>1</sup>

### **When to Stop Therapy**

Information regarding when to stop preventive treatment is discussed in the following two guidelines:

- The 2012 CHS guideline for the management of episodic migraine contains the following consensus recommendations in the context of the availability of only oral medications for EM at that time:
  - For purposes of determining whether a medication is ineffective for a patient, an adequate trial of an oral prophylactic medication is considered to be at least 2 months at the target dose or the maximum tolerated dose.<sup>19</sup> Authors recommended that patients keep a headache diary /calendar in order to best track their response to therapy.
  - “After 6 to 12 months of successful prophylactic therapy, consideration should be given to tapering and discontinuing the prophylactic medication in many patients, although others may benefit from a much longer duration of prophylactic therapy. If headache frequency increases as the prophylactic drug dosage is reduced, the dosage can be increased again or the drug restarted if it has been discontinued.”<sup>19</sup>
- The 2012 NICE guidance on the use of OBTA for CM recommends stopping OBTA if there is not at least a 30% reduction in headache days per month after two treatment cycles. Discontinuation is also recommended once the patient’s symptoms change to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months; although, some patients may need to be restated if they convert back to CM following discontinuation.

**Table 1** provides a summary of the recommended therapies among clinical treatment guidelines for migraine prevention. All were published prior to the approval of CGRP antagonists.

Table 1. Recommended Agents for Migraine Prevention Among Treatment Guidelines	
Professional Organization	Statements
❖ Guideline Title	
<b>American Academy of Neurology and the American Headache Society</b>	<b>Guideline Background</b>
❖ Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults <sup>11</sup> (2012)	<p>Literature was searched in MEDLINE, PsycINFO, and CINAHL from 1999 to May 2007 to identify RCTs to determine the effectiveness of pharmacologic therapies for migraine prevention, as measured by reduced migraine attack frequency, reduced number of migraine days, or reduced attack severity</p> <ul style="list-style-type: none"> <li>• Define the safety profile of these pharmacological treatment options</li> </ul> <p>The literature search was updated through May 2009 in MELINE only.</p>
	<b>Recommendations</b>
	<p>Medications with <b>Level A evidence</b> (established as effective; with ≥2 Class I trials) and that should be offered for migraine prevention: divalproex sodium, sodium valproate, topiramate metoprolol, propranolol, timolol</p> <ul style="list-style-type: none"> <li>- For short-term menstrual migraine prevention: frovatriptan</li> </ul> <p>Medications with <b>Level B evidence</b> (probably effective; 1 Class I or 2 Class II studies) and that should be considered for migraine prevention: amitriptyline, venlafaxine, atenolol, nadolol</p> <ul style="list-style-type: none"> <li>- For short-term menstrual migraine prevention: naratriptan and zolmitriptan</li> </ul> <p>Medications with <b>Level C evidence</b> (possibly effective; 1 Class II study) and may be considered for migraine prevention: lisinopril, candesartan, clonidine, guanfacine, carbamazepine, nebivolol, pindolol, and cyproheptadine</p> <p>Medications with <b>Level U evidence</b> (inadequate or conflicting data to support or refute medication use): acetazolamide, acenocoumarol, coumadin, picotamide, fluvoxamine, fluoxetine, gabapentin, protriptyline, bisoprolol, nifedipine, nifedipine, nimodipine, verapamil, cycloandelate</p> <p>Other medications that are established as <b>possibly or probably ineffective</b>: lamotrigine, clomipramine, acebutolol, clonazepam, nabumetone, oxcarbazepine, telmisartan</p>
<b>National Institute for Health and Care Excellence</b>	<b>Migraine (with or without aura) Preventive Therapy</b>
❖ Headaches in over 12s: diagnosis and management; CG150 <sup>18</sup> (2012, updated in 2015)	<ul style="list-style-type: none"> <li>- The following medications should be offered and the decision should be based on the patient’s preference, comorbidities and risk of adverse events: <ul style="list-style-type: none"> <li>• Topiramate (warn about the risk of fetal malformations and reduction of the effectiveness of hormonal contraceptives with this medication)</li> <li>• Propranolol</li> <li>• Amitriptyline</li> </ul> </li> <li>- If patients are already on another form of prophylaxis that is effective for them, continue the current treatment</li> <li>- Do not offer gabapentin for the prophylactic treatment of migraine</li> <li>- Re-assess the need for prophylactic therapy 6 months after initiation</li> </ul>



Table 1. Recommended Agents for Migraine Prevention Among Treatment Guidelines

Professional Organization ❖ Guideline Title	Statements
<p><b>Canadian Health Society Guideline for Migraine Prophylaxis</b></p> <p>❖ Canadian Headache Society Guideline for Migraine Prophylaxis<sup>19</sup> (2012)</p>	<p>This guideline applies to patients with episodic migraine (headache on no more than 14 days a month) who suffer from a significant degree of disability from these attacks and for whom abortive medications do not provide sufficient relief to minimize migraine-related disability or who are at high risk of medication overuse headache or intolerable side-effects due to use of acute treatments.</p> <p>Prophylactic options with high-quality evidence showing efficacy:</p> <ul style="list-style-type: none"> <li>• Beta-blockers: Propranolol (target dose 80 to 160 mg/d), and metoprolol (target dose 100 to 200 mg/d); both with “strong recommendation”</li> <li>• Topiramate (target dose of 100 mg/d): authors assign a “strong recommendation” for use of this drug, since its risk benefit profile is positive</li> <li>• Amitriptyline (10 to 100 mg/d); “strong recommendation”</li> <li>• Divalproex (500 to 1500 mg/d); authors assign a “weak recommendation” to this drug due to the risk benefit profile of divalproex. Some adverse effects include weight gain, reversible tremor, hair loss, and teratogenicity</li> </ul> <p>Prophylactic options with moderate-quality evidence showing efficacy:</p> <ul style="list-style-type: none"> <li>○ Gabapentin (at least 1,200 mg/d) : “strong recommendation”</li> <li>○ Nadolol (80 to 160 mg/d): “strong recommendation”</li> <li>○ Candesartan (16 mg/d): “strong recommendation”</li> </ul> <p>Prophylactic options with low-quality evidence showing efficacy: venlafaxine, verapamil, lisinopril</p>
<p><b>American Academy of Neurology</b></p> <p>❖ Practice Parameter: Pharmacological treatment of migraine headache in children and adolescents (2004)<sup>5</sup></p>	<p style="text-align: center;"><b>Recommendations</b></p> <ul style="list-style-type: none"> <li>- “There is insufficient evidence to make any recommendations concerning the use of amitriptyline, divalproex sodium, topiramate, or levetiracetam...”</li> <li>- Recommendations were not made concerning propranolol or trazodone for preventive therapy as the evidence is conflicting.</li> <li>- Pizotifen and nimodipine and clonidine lack have supportive evidence for efficacy and are not recommended.</li> </ul>
<b>Guidance for the Use of OnabotulinumtoxinA</b>	
<p><b>American Academy of Neurology</b></p> <p>❖ Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache<sup>13</sup> (2016)</p>	<p>OBTA is effective and safe for the reduction of headache days and probably effective for improving quality of life for patients with chronic migraine. Authors state that there is insufficient evidence comparing OBTA to topiramate for chronic migraine.</p>

Table 1. Recommended Agents for Migraine Prevention Among Treatment Guidelines

Professional Organization ❖ Guideline Title	Statements
<b>National Institute for Health and Care Excellence</b>  <ul style="list-style-type: none"> <li>Botulinum toxin type A for the prevention of headaches in adults with chronic migraine; Technology appraisal guidance [TA260]<sup>20</sup> (2012, updated 2015)</li> </ul>	<p>OnabotulinumtoxinA is a recommended option for the treatment of chronic migraine that has not responded to at least three prior pharmacological prophylactic therapies (only if the patient is appropriately managed for medication overuse)</p> <ul style="list-style-type: none"> <li>Chronic migraine is defined as having headaches on at least 15 days per month of which at least 8 days are with migraine</li> </ul> <p>Treatment with OBTA should be stopped if there is not at least a 30% reduction in headache days per month after two treatment cycles, or if the patient’s symptoms have changed to episodic migraine (defined as fewer than 15 headache days per month) for three consecutive months. Nonetheless, patients should have the option to continue treatment until they and their clinician consider it appropriate to stop if the circumstance falls outside of these recommendations.</p>

Abbreviations: OBTA, onabotulinumtoxinA, RCT, randomized controlled trial

### Safety Information for Other Medications Approved for Migraine Prevention

Long-term adherence to the oral migraine preventive agents is low in patients with chronic migraine (29% at 6 months, and 20% at 12 months)<sup>21</sup> due to a mix of factors including adverse reactions and inadequate response to therapy. Poor persistence and adherence to oral migraine-preventive agents remains a topic of discussion, as there is much room for improvement.<sup>21-24</sup>

The anticonvulsants, divalproex and topiramate, can produce neurological and gastrointestinal side effects, and can cause fetal harm (black box warning for divalproex).<sup>25,26</sup> Paresthesia is common with topiramate, although, cognitive dysfunction is the main adverse event-related reason for discontinuation (eg, confusion, psychomotor slowing, impaired concentration and memory, word-finding difficulty).<sup>27</sup> In placebo-controlled trials, 20% of topiramate-treated patients withdrew due to adverse events.<sup>28</sup> Weight gain, tremor, and alopecia can occur with long-term use of divalproex, while gastrointestinal events can cause significant distress initially (but may lessen after 6 months of use and with slow titration).<sup>29</sup> Common adverse events involved with beta-blockers include fatigue, reduced exercise tolerance, hypotension, sexual dysfunction, sleep disturbance, lightheadedness, disorientation, and gastrointestinal side effects.

Regarding the intramuscular injection product for chronic migraine, OBTA was well tolerated, with a low discontinuation rate due to adverse events of about 4% in pivotal studies.<sup>30</sup> Labeled adverse events occurring in ≥5% patients and more often than placebo include neck pain and headache.<sup>30</sup>

## FDA-Approved Monoclonal Antibodies for Migraine Prevention

The newly approved monoclonal antibodies have been developed specifically to target the pathway involving calcitonin gene-related peptide (CGRP) which is implicated as part of migraine pathogenesis.<sup>10,31</sup> Erenumab binds to the CGRP receptor and antagonizes CGRP effects.<sup>10</sup> Fremanezumab and galcanezumab, bind to CGRP ligand, antagonizing its action at the CGRP receptor.<sup>31,32</sup> Erenumab was the first-in-class product approved in May of 2018, followed by the approvals of fremanezumab and galcanezumab in September.

These CGRP antagonists are indicated for the adult population and are administered subcutaneously, offering less frequent dosing compared to daily-dosed, oral options. Erenumab and galcanezumab have once monthly dosing, and fremanezumab is administered once monthly or quarterly. For erenumab, there are two dosages that can be given once monthly (70 mg or 140 mg). One dosage is specified per administration interval for galcanezumab and fremanezumab (see Table 2).

The package insert for erenumab does not specify for whom or in what circumstance it is recommended to up-titrate to the higher dosage. Information regarding the higher dosage was found in the FDA Summary Review as follows:

“The 140-mg dose shows small numerical advantages on the primary and key secondary endpoints in one study (296) [of EM patients], and on the secondary endpoint of the proportion of subjects with at least a 50% reduction in MMD [monthly migraine days] from baseline in another study (295) [of CM patients]. Although superiority of the 140-mg dose has not been established over the 70-mg dose, it is possible that some patients may benefit from an increase from 70 to 140 mg.”<sup>10</sup>

There are no known drug interactions with CGRP antagonists. Renal or hepatic dosage adjustments are unnecessary. **Table 2** provides select product information from the FDA-approved product labeling.

Table 2. FDA-approved Monoclonal Antibodies for Migraine Prevention<sup>31-33</sup>

	<b>Erenumab-aooe</b> (Aimovig)	<b>Fremanezumab-vfrm</b> (Ajovy)	<b>Galcanezumab-gnlm</b> (Emgality)
<b>Approved Indication</b>	Migraine prevention in adults (episodic and chronic migraine)		
<b>Formulation and Storage</b>	<ul style="list-style-type: none"> <li>• 70 mg/mL in a single-dose prefilled SureClick autoinjector</li> <li>• 70 mg/mL in a single-dose prefilled syringe</li> <li>• Refrigerate (36 to 46°F); if removed from refrigeration, should be kept at room temperature and used within 7 days</li> </ul>	<ul style="list-style-type: none"> <li>• 225 mg/1.5 mL in a single-dose prefilled syringe</li> <li>• Refrigerate (36 to 46°F); if removed from refrigeration, should be kept at room temperature and used within 24 hours</li> </ul>	<ul style="list-style-type: none"> <li>• 120 mg/mL in a single-dose prefilled pen</li> <li>• 120 mg/mL in a single-dose prefilled syringe</li> <li>• Refrigerate (36 to 46°F); if removed from refrigeration, should be kept at room temperature and used within 7 days</li> </ul>
<b>Dosage and Administration</b>	Initiate as 70 mg injected subcutaneously once monthly. Some patients benefit from a dose of 140 mg administered as 2 consecutive subcutaneous injections of 70 mg each.	Administer 225 mg monthly OR 675 mg every 3 months (administered as 3 consecutive 225 mg injections)	Initiate as 240 mg subcutaneous loading dose (2 consecutive injections of 120 mg each), followed by once monthly doses of 120 mg
<b>Metabolism</b>	Not metabolized by CYP-P450 enzymes		
	Eliminated through saturable binding to CGRP receptor and through proteolytic pathways	Eliminated through proteolytic pathways	
<b>Half-life</b>	28 days	31 days	27 days
<b>Tmax</b>	6 days	5 to 7 days	5 days
<b>Special Population Considerations</b>	<p>A. Pregnancy/Lactation: There is no data in pregnant women or their offspring. No adverse effects in offspring from animal studies were observed. There is no data on lactation excretion.</p> <p>B. Safety and effectiveness in the pediatric population have not been established.</p> <p>C. Renal or hepatic impairment is not expected to affect the pharmacokinetics of CGRP antagonists.</p> <p>D. Geriatric Use: studies included insufficient number of patients 65 years and older to determine if they respond differently compared to younger patients.</p>		
<b>Common Adverse Reactions</b>	Reported in >3% of patients and more often than placebo: injection site reaction and constipation	Reported in ≥5% and greater than event rate in placebo arm: injection site reactions	Reported in ≥2% and at least 2% greater than event rate in placebo arm: injection site reactions
Abbreviations: Tmax, time to maximum concentration			

## **Efficacy**

There are no randomized, controlled trials that directly compare the CGRP antagonists at this time. When examining efficacy comparisons from placebo-controlled trials, it is important to consider the *difference in effect* between the active and placebo arms because there is usually a strong placebo effect in migraine-prevention studies.<sup>9,34,35</sup> Keep in mind that it is unscientific to directly compare the effect magnitude of active treatments based on how they performed in different trials versus placebo, because there may be considerable differences in patient populations, trial designs, and endpoint definitions for outcomes that are unaccounted for when making such an indirect comparison. In the *Episodic Migraine* and *Chronic Migraine* subsections below, results reported for the effect difference between CGRP antagonists versus placebo were statistically significant.

### **Episodic Migraine**

In pivotal clinical trials leading to the approval of the CGRP antagonists, treatment generally led to about 1 to 2 fewer mean monthly migraine days (mMMD) compared to placebo (primary endpoint) for patients with EM, while the mMMD change from the patients' baseline ranged from about 3 to 5 mMMD for the CGRP antagonists.<sup>31-33</sup> Other key secondary endpoints significantly favored erenumab, galcanezumab, and fremanezumab over placebo in terms of response rates (eg, at least a 50% reduction in mMMD), reduction in acute migraine-specific medications (eg, triptans and ergots), and improvement in physical functioning and/or disability score and status of illness (measured by various assessment tools such as the Migraine Physical Function Impact Diary, functional impairment assessment in the Migraine-Specific Quality of Life Questionnaire [MSQ], Patient Global Impression of Severity [PSI-S], Migraine Disability Assessment [MIDAS], and Headache Impact Test [HIT-6]).

#### **Erenumab**

For the two pivotal clinical trials of adults with EM, patients had to have a history of migraine for a least 12 months prior to the study and 4 to 14 monthly migraine days (MMD) in the 3 months preceding the screening phase.<sup>36,37</sup> One study involved a treatment duration of 6 months and the other was 3 months.<sup>33</sup> A subset of patients was allowed to use up to one preventive-migraine medication concomitantly in each study.<sup>33,36,37</sup> Excluded patients were those with migraine onset after 50 years of age, history of hemiplegic migraine or cluster headache, major pre-existing cardiovascular disease 12 months prior to screening, botulinum toxin use within 4 months of the baseline phase, and those with drug or alcohol abuse.<sup>33,36,37</sup>

For the primary endpoint (change in mMMD from baseline), erenumab further reduced mMMD by about 1 to 2 more days compared to placebo in the pivotal EM trials.<sup>33,36,37</sup> Treatment arms improved by about 3 to 4 mMMD from baseline, while placebo arms improved by about 2 mMMD from baseline. Forty to 50% of patients receiving erenumab experienced at least a 50% reduction in mMMD (10% to 23% difference from placebo). Treatment and placebo groups had

a baseline rate of about 8 MMD.<sup>33,36,37</sup> In these studies, about 40% of patients had prior use of a preventive medication and 3% to 7% of patients had current at treatment entry.<sup>36,37</sup>

### Fremanezumab

The pivotal clinical trial for adults with EM included patients with a history of migraine for at least 1 year prior to screening, with headache 6 to 14 days in the 28-day period before treatment; at least 4 of these headaches had to be classified as migraine, probable migraine, or require the use of triptans or ergot derivatives.<sup>38</sup> A subset of patients was allowed to use one concomitant preventive medication. Patients were excluded if they had migraine onset after 50 years of age, received botulinum toxin within 4 months before screening, were pregnant, or if they had significant cardiovascular disease.<sup>31,38</sup>

Treatment with fremanezumab led to about 1 to 2 fewer mMMD (primary endpoint) compared to placebo. Treatment arms improved by about 3 to 4 mMMD from baseline, while the placebo arm improved by about 2 mMMD from baseline. Forty-five to 48% of patients receiving fremanezumab experienced at least a 50% reduction in mMMD (17% to 20% difference from placebo), over a 3 month treatment period.<sup>31,38</sup> Treatment and placebo groups had a baseline rate of about 9 MMD and about 20% entered the treatment phase on a preventive medication.<sup>38</sup>

### Galcanezumab

In the two pivotal trials of adults with EM, patients had to have a history of migraine for at least 1 year prior to the study and migraine onset before 50 years old.<sup>39,40</sup> To be included, patients had to experience 4 to 14 migraine headache days per month (allowing for probable migraine), with at least 2 migraine attacks occurring during the 30 to 40 days baseline period. Unlike the previously discussed EM trials for erenumab and fremanezumab, patients were not allowed concomitant use of any other preventive-migraine medication during the study. Additionally, patients were not allowed to use OBTA in the 4 months prior to screening or during study. Studies excluded patients with medication overuse headache, significant ECG abnormalities, or history of any of the following within 6 months of screening: stroke, myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, deep vein thrombosis, or pulmonary embolism.<sup>32</sup>

Treatment with galcanezumab led to about 2 fewer mMMD (primary endpoint), compared to placebo. Treatment arms improved by about 4 to 5 mMMD from baseline, while placebo arms improved by about 2 to 3 mMMD from baseline. Sixty to 62% of patients experienced at least a 50% reduction in mMMD (23% difference from placebo), over a 6 month treatment period.<sup>32</sup> Study arms had a baseline rate of about 9 MMD. Additional responder secondary endpoints were evaluated including the proportion of patients with at least a 75% or 100% reduction in mMMD: 34% to 39% of galcanezumab-treated patients experienced a 75% mMMD reduction from baseline (16% to 20% difference from placebo), and 12% to 16% of treated patients experienced a 100% mMMD reduction from baseline (6% to 10% difference from placebo).<sup>32</sup>

## Chronic Migraine

In pivotal trials of the CGRP antagonists, compared to placebo, active treatment generally led to about 2 to 3 fewer MMD for patients with CM, over a treatment period of 3 months.<sup>31-33</sup> Changes from baseline ranged from about 5 to 7 mMMD for the CGRP antagonists.<sup>31-33</sup>

### Erenumab

In the pivotal trial of patients with CM, patients were required to have a history of migraine for at least 1 year and meet the ICDH-3 criteria for CM in each of the 3 months prior to screening.<sup>41</sup> Patients with overuse headache were allowed.<sup>41</sup> Exclusion criteria were onset of migraine at 50 years of age or older, history of cluster headache, history of hemiplegic migraine, or persistent migraine with no pain-free periods. Patients with a history of myocardial infarction, stroke, transient ischemic attacks, unstable angina, revascularization procedures within 12 months of screening, or drug/alcohol abuse were also excluded.<sup>10,33</sup> Concomitant use of other preventive therapies was not allowed and botulinum toxin had to be discontinued at least 4 months before the baseline phase.<sup>41</sup>

Compared to placebo, treatment with erenumab led to about 2.5 fewer mMMD (primary endpoint). Treatment arms improved by about 7 mMMD from baseline, while the placebo arm improved by about 4 mMMD from baseline. About 16% to 17% more erenumab-treated patients experienced at least a 50% reduction in mMMD over a 3 month treatment period compared to the placebo arm; about 40% of erenumab-treated patients met the 50% MMD reduction threshold.<sup>33</sup> The baseline MMD was about 18 for all study arms and 41% of patients in the study had medication overuse.<sup>33,41</sup>

### Fremanezumab

Patients in the CM pivotal study for fremanezumab were included if they had a history of migraine for at least 12 months, and whom also met criteria for CM in the 28-day pre-intervention period.<sup>42</sup> A subset of patients was allowed to use up to one oral migraine-preventive medication as long as the dose was stable for at least 2 months before the pre-intervention period. OBTA had to be discontinued 4 months before screening. Pregnancy or nursing females, or patients with history of significant cardiovascular disease, vascular ischemia, or thrombotic events were excluded.<sup>31</sup> The baseline mMMD was about 16 for the study arms and about 21% of patients entered the treatment phase on another preventive medication.<sup>31,42</sup>

The primary endpoint was the change from baseline in the mean monthly number of headache days of at least moderate severity (mMHD<sub>ms</sub>) over the 3 month treatment period.<sup>31</sup> Fremanezumab reduced the mMHD<sub>ms</sub> significantly more than placebo, by about 2 more days. The mMMD reduction from baseline was a secondary endpoint. Compared to placebo, treatment with fremanezumab led to about 2 fewer mMMD; treatment arms improved by about 5 mMMD from baseline, while the placebo arm improved by about 3 mMMD from

baseline. Between 20% and 23% more fremanezumab-treated patients experienced at least a 50% reduction in mMHD<sub>ms</sub> compared to placebo; about 40% of fremanezumab-treated patients met the 50% monthly headache day reduction threshold.<sup>31</sup>

## Galcanezumab

For the pivotal clinical trial of patients with CM, patients had to have CM diagnosed and demonstrate  $\geq 15$  headache days per month (at least 8 migraine days) for at least 3 months before screening.<sup>43</sup> Patients were also required to have at least 1 headache free day per month. Patients were excluded if migraine onset occurred after 50 years old, or if they had cluster headache, head or neck trauma in prior 6 months, posttraumatic headache, unstable medical or psychiatric conditions, or history of substance abuse or dependence in the past year. Patients with history of any of the following within 6 months of screening were also excluded: stroke, ECG abnormalities, myocardial infarction, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, deep vein thrombosis, or pulmonary embolism.<sup>32</sup>

Patients were allowed one concomitant therapy with propranolol or topiramate if the dose had been stable for the 2 months prior to the baseline period; about 15% of patients entered the treatment phase on one of these therapies<sup>43</sup>

For the primary endpoint, compared to placebo, treatment with galcanezumab (120 mg dosage) led to about 2 fewer mMMD.<sup>32</sup> The treatment arm improved by about 5 mMMD from baseline, while the placebo arm improved by about 3 mMMD from baseline. The baseline mMMD was about 19 for the study arms. Approximately 13% more galcanezumab-treated patients experienced at least a 50% reduction in mMMD over the 3 month treatment period than in the placebo arm; 28% of galcanezumab-treated patients met the 50% monthly headache day reduction threshold.<sup>32</sup>

## Other Published Prospective Studies

- A phase 3, randomized, placebo-controlled trial (LIBERTY) showed that erenumab was effective for adults who had inadequate response (either by efficacy, tolerability, or both) to 2 to 4 previously tried migraine-preventive therapies.<sup>44</sup>
- A long-term open-label study of 12 months treatment with galcanezumab has been published that included patients with 4 or more migraine headache days per month (see safety section for more information).<sup>45</sup>



## Safety

The most common adverse reactions were injection site reactions (eg, pain, erythema) that occurred in about 5-6% of patients treated with erenumab (vs. 3% with placebo), 43-45% with fremanezumab (vs. 38% with placebo), and 18% with galcanezumab (vs. 13% with placebo).<sup>31-33</sup> Adverse event warnings included in product labeling are (a) possible hypersensitivity, which can be delayed following injection or prolonged due to the long half-life of these agents, and (b) the development of drug neutralizing-antibodies which is possible at any time during therapy. Overall, the monoclonal antibodies were well tolerated with low study drop-out rates ( $\leq 2\%$ ) due to adverse events in the double-blind pivotal trials.<sup>31-33</sup> The only contraindications include hypersensitivity to active ingredients or excipients, labeled for galcanezumab and fremanezumab.

**Table 3** provides information regarding anti-drug antibody development from product prescribing information.

Table 3. Labeled Warning Information

<b>Erenumab-aooe</b> (Aimovig)	<b>Fremanezumab-vfrm</b> (Ajovy)	<b>Galcanezumab-gnlm</b> (Emgality)
The incidence of anti-drug antibodies in controlled studies is 6.2% (48/778) with the 70 mg/month dose (2 patients had in vitro neutralizing activity) and 2.6% (13/504) with 140 mg/month (no patients had in vitro neutralizing activity).	In the ongoing long-term study 1.6% of patients developed drug antibodies; about 60% of them had drug neutralizing activity	Anti-drug antibody occurrence was about 4.8% to 12.5% of patients with higher rates occurring with longer treatment duration, most which were drug neutralizing

## Long-Term Use

An open-label, phase 3 trial with galcanezumab has been published, showing safety data for 12 months of treatment of 135 patients with either EM or CM (mean baseline of 11 MMD).<sup>45</sup> Regarding the group treated with galcanezumab 120 mg per month, 28% of patients did not complete the 12 month-treatment phase, and 4.7% discontinued treatment due to an adverse event. Mean treatment compliance was 96% for those completing 12 months of galcanezumab 120 mg/month. Treatment emergent adverse events occurring in  $\geq 10\%$  of patients on the 120 mg/month dose were injection site pain, nasopharyngitis, injection site reaction, and sinusitis. Authors noted that there were only "... temporary and minimal changes from baseline in laboratory values, vital signs, ECG parameters, and weight."<sup>45</sup>

## Medicaid Utilization

Based on Medicaid pharmacy claim records, CGRP antagonists have not yet been dispensed to the fee-for-service population.

## Potential Prior Authorization Criteria and Discussion Topics

- Require that patients receive CGRP antagonists for the approved use (ie, prevention of migraine in adults). Other experimental applications include hot flashes,<sup>46</sup> PPTH, cluster headaches<sup>47</sup>, however, are not yet approved indications for any of the reviewed monoclonal antibodies. Future label extensions may follow as additional clinical studies in other populations are presented to the FDA.
- May consider the following:
  - Requiring patients to demonstrate a history of migraine for at least 1 year prior to starting a CGRP antagonist; this was an inclusion criteria in most pivotal clinical trials.<sup>10,48,49</sup>
  - Requiring patients to have at least 4 migraine days or probable migraine days per month demonstrated in the X (eg, 3) months prior to CGRP-antagonist initiation.
  - You may also refer to page 5 regarding information in guidelines about when to start preventive therapy for episodic migraine; however, note that these guidelines pre-date approvals of the CGRP antagonists and do not cover CM.
- May limit concomitant use with onabotulinumtoxinA (Botox). Most clinical trials allowed for concomitant use of another preventive therapy, excluding onabotulinumtoxinA.
  - Regarding use of oral agents, consider that patients may be using antihypertensives, anticonvulsants, or antidepressants primarily for other indications. The co-morbidity profile of a patient may preclude their ability to discontinue use of a certain number of oral migraine-preventive agents.
- For erenumab, consider allowing patients to start at 70 mg/month, then increase to 140 mg/month if patients have an inadequate response after adherence to at least X (eg, 3) months at the lower dosage. Alternatively, you may wish to leave the decision regarding up-titration to the provider. The labeling for erenumab does not provide a recommendation on when to increase the dose; nonetheless, prescribing information mentions that “serum trough concentrations approached steady state by 3 months of dosing.”<sup>33</sup>
- For patients whose prescriber cannot document a positive response to therapy after 6 months of treatment, consideration should be given to discontinue the medication.

- If a requirement of trial and failure of a certain number of drugs or drug classes is considered for eligibility, you may wish to refer to Table 4 to help choose appropriate medications. Highlighted in blue are those medications that are referred to in the 2012 AAN/AHS guideline or the 2012 Canadian Health Society guideline as having level A or B evidence or moderate to high quality evidence, respectively, for the prevention of episodic migraine in adults. Also consider that onabotulinumtoxinA and topiramate have been shown to be efficacious in randomized, placebo-controlled trials of patients with chronic migraine.<sup>12,14,15</sup>

Table 4. Evidence Rankings for Drug Efficacy in Episodic Migraine Prevention Treatment Guidelines

<b>Medication Categories</b>	<b>2012 AAN/AHS Guideline<sup>a</sup></b>	<b>2012 Canadian Guideline</b>
Antihypertensives:  Beta-Blockers, ACE Inhibitors, ARBs	Level A evidence (established as effective) metoprolol, propranolol, timolol	High quality evidence for effectiveness metoprolol, propranolol
	Level B evidence (probably effective) atenolol, nadolol	Moderate quality evidence nadolol, candesartan
	Level C evidence (possibly effective) nebivolol, pindolol, lisinopril, candesartan	Low quality evidence lisinopril
Anticonvulsants	Level A evidence (established as effective) divalproex, sodium valproate, topiramate	High quality evidence for effectiveness divalproex, topiramate
	Level C evidence (possibly effective) carbamazepine	Moderate quality evidence gabapentin <sup>b</sup> ,
Antidepressants		High quality evidence for effectiveness amitriptyline
	Level B evidence (probably effective) amitriptyline, venlafaxine	
		Low quality evidence venlafaxine ER
Others:  Alpha Antagonists, Antihistamines, Calcium Channel Blockers	Level C evidence (possibly effective) clonidine, guanfacine, cyproheptadine,	Low quality evidence verapamil <sup>b</sup>

<sup>a</sup> Medications listed in the AAN/AHS guidelines that have inadequate or conflicting data to support or refute their use, or that are established as possibly or probably ineffective are not represented in this chart. See Table 1 of the report for a list of these agents.

<sup>b</sup> Gabapentin and verapamil are classified as having inadequate or conflicting data to support or refute medication use in the 2012 AAN/AHS guideline.

Abbreviations: ACE, angiotensin converting enzyme; ARBs, Angiotensin II Receptor Blockers

## Summary

Migraine headache is a common neurological condition causing considerable burden to patients. About 20% or 50% of patients with episodic migraine or chronic migraine suffer from moderate to severe headache-related disability, respectively.<sup>6</sup> Chronic migraine accounts for about 8% of the total migraine cases.<sup>6,7</sup> Guidelines for the management of migraine pre-date the approvals of the CGRP antagonists.

The efficacy of the CGRP antagonists was demonstrated for both episodic migraine and chronic migraine prevention in the adult population. These subcutaneous-injectable products allow for less frequent dosing intervals compared to the daily dosed, oral migraine-preventive therapies. Each CGRP antagonist can be administered once monthly; additionally, fremanezumab can be dosed once quarterly. Erenumab has two dosage options for the monthly administration interval (70 mg/month or 140 mg/month). Most pivotal studies required that patients have a history of migraine for at least 1 year, along with thresholds for monthly migraine days to be met in order to enter the treatment phase (eg, 4 MMD for EM patients, and 15 MMD for CM patients). The CGRP antagonists have a positive tolerability profile, with  $\leq 2\%$  of patients in pivotal trials withdrawing from study due to adverse events. Moreover, no drug-drug interactions are known of for this drug class.

## References

1. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(6):754-762.
2. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. 2001;41(7):646-657.
3. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. *Headache*. 2015;55(1):21-34.
4. Blumenfeld AM, Varon SF, Wilcox TK, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). *Cephalalgia*. 2011;31(3):301-315.
5. Lewis D, Ashwal S, Hershey A, Hirtz D, Yonker M, Silberstein S. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. *Neurology*. 2004;63(12):2215-2224.
6. Buse DC, Manack AN, Fanning KM, et al. Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study. *Headache*. 2012;52(10):1456-1470.
7. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
8. Lipton RB, Manack Adams A, Buse DC, Fanning KM, Reed ML. A Comparison of the Chronic Migraine Epidemiology and Outcomes (CaMEO) Study and American Migraine Prevalence and Prevention (AMPP) Study: Demographics and Headache-Related Disability. *Headache*. 2016;56(8):1280-1289.
9. Silberstein S, Tfelt-Hansen P, Dodick DW, et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. *Cephalalgia*. 2008;28(5):484-495.
10. Center for Drug Evaluation and Research. Drugs@FDA: Drug Approval Package: Aimovig (erenumab-aooe) injection, Summary Review. Application Number 761077. May 15, 2018. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/761077Orig1s000SumR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761077Orig1s000SumR.pdf). Accessed October 10, 2018.
11. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78(17):1337-1345.
12. Starling AJ, Dodick DW. Best practices for patients with chronic migraine: burden, diagnosis, and management in primary care. *Mayo Clin Proc*. 2015;90(3):408-414.
13. Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;86(19):1818-1826.
14. Diener HC, Bussone G, Van Oene JC, Lahaye M, Schwalen S, Goadsby PJ. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. *Cephalalgia: An International Journal Of Headache*. 2007;27(7):814-823.

15. Silberstein SD, Lipton RB, Dodick DW, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. *Headache*. 2007;47(2):170-180.
16. Barnes NP. Migraine headache in children. *BMJ clinical evidence*. 2015;2015.
17. Mulleners WM, McCrory DC, Linde M. Antiepileptics in migraine prophylaxis: an updated Cochrane review. *Cephalalgia : an international journal of headache*. 2015;35(1):51-62.
18. NICE Guidance. *Headaches in over 12s: diagnosis and management; CG150*. Published date: September 2012, last updated November 2015. National Institute for Health and Care Excellence.
19. Pringsheim T, Davenport W, Mackie G, et al. Canadian Headache Society guideline for migraine prophylaxis. *The Canadian journal of neurological sciences Le journal canadien des sciences neurologiques*. 2012;39(2 Suppl 2):S1-59.
20. NICE Guidance. *Botulinum toxin type A for the prevention of headaches in adults with chronic migraine: TA260*. Published date June 2012. . National Institute for Health and Care Excellence.
21. Hepp Z, Dodick DW, Varon SF, Gillard P, Hansen RN, Devine EB. Adherence to oral migraine-preventive medications among patients with chronic migraine. *Cephalalgia*. 2015;35(6):478-488.
22. Hepp Z, Bloudek LM, Varon SF. Systematic review of migraine prophylaxis adherence and persistence. *Journal of managed care pharmacy : JMCP*. 2014;20(1):22-33.
23. Ramsey RR, Ryan JL, Hershey AD, Powers SW, Aylward BS, Hommel KA. Treatment adherence in patients with headache: a systematic review. *Headache*. 2014;54(5):795-816.
24. Seng EK, Buse DC, Klepper JE, et al. Psychological Factors Associated With Chronic Migraine and Severe Migraine-Related Disability: An Observational Study in a Tertiary Headache Center. *Headache*. 2017;57(4):593-604.
25. *Depakote ER (divalproex sodium) tablet ER [package insert]*. North Chicago, IL; Abbvie Inc. Revised October 2017.
26. *Topiramate extended-release capsule [package insert]*. Pennington, NJ; Zydus Pharmaceuticals Inc.; Revised May 2017.
27. Silberstein SD. Topiramate in Migraine Prevention: A 2016 Perspective. *Headache*. 2017;57(1):165-178.
28. Linde M, Mulleners WM, Chronicle EP, McCrory DC. Topiramate for the prophylaxis of episodic migraine in adults. *The Cochrane database of systematic reviews*. 2013(6):CD010610.
29. Silberstein SD. Preventive Migraine Treatment. *Continuum (Minneapolis, Minn)*. 2015;21(4 Headache):973-989.
30. *Botox (onabotulinumtoxinA) for injection [package insert]*. Madison, NJ; Allergan USA Inc.; Revised May 2018.
31. *Ajovy (fremanezumab-vfrm) injection [package insert]*. North Wales, PA; Teva Pharmaceuticals USA, Inc. September 2018.
32. *Emgality (galcanezumab-gnlm) injection [package insert]*. Indianapolis, IN: Eli Lilly and Company. Revised September, 2018.
33. *Aimovig (erenumab-aooe) injection [package insert]*. Thousand Oaks, CA; Amgen Inc. Revised May 2018.
34. Meissner K, Fassler M, Rucker G, et al. Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. *JAMA internal medicine*. 2013;173(21):1941-1951.
35. Hougaard A, Tfelt-Hansen P. Are the current IHS guidelines for migraine drug trials being followed? *J Headache Pain*. 2010;11(6):457-468.
36. Goadsby PJ, Reuter U, Hallstrom Y, et al. A Controlled Trial of Erenumab for Episodic Migraine. *The New England journal of medicine*. 2017;377(22):2123-2132.
37. Dodick DW, Ashina M, Brandes JL, et al. ARISE: A Phase 3 randomized trial of erenumab for episodic migraine. *Cephalalgia*. 2018;38(6):1026-1037.

38. Dodick DW, Silberstein SD, Bigal ME, et al. Effect of Fremanezumab Compared With Placebo for Prevention of Episodic Migraine: A Randomized Clinical Trial. *Jama*. 2018;319(19):1999-2008.
39. Skljarevski V, Matharu M, Millen BA, Ossipov MH, Kim BK, Yang JY. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia*. 2018;38(8):1442-1454.
40. Stauffer VL, Dodick DW, Zhang Q, Carter JN, Ailani J, Conley RR. Evaluation of Galcanezumab for the Prevention of Episodic Migraine: The EVOLVE-1 Randomized Clinical Trial. *JAMA neurology*. 2018;75(9):1080-1088.
41. Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. *The Lancet Neurology*. 2017;16(6):425-434.
42. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the Preventive Treatment of Chronic Migraine. *The New England journal of medicine*. 2017;377(22):2113-2122.
43. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. *Neurology*. 2018.
44. Reuter U, Goadsby PJ, Lanteri-Minet M, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *Lancet (London, England)*. 2018.
45. Camporeale A, Kudrow D, Sides R, et al. A phase 3, long-term, open-label safety study of Galcanezumab in patients with migraine. *BMC neurology*. 2018;18(1):188.
46. U.S. National Library of Medicine, ClinicalTrials.gov. Study of Erenumab (AMG 334) in Women With Hot Flashes. 2013;  
<https://clinicaltrials.gov/ct2/show/NCT01890109?term=erenumab&rank=5>.
47. Schuster NM, Rapoport AM. Calcitonin Gene-Related Peptide-Targeted Therapies for Migraine and Cluster Headache: A Review. *Clin Neuropharmacol*. 2017;40(4):169-174.
48. Center for Drug Evaluation and Research. Drugs@FDA: Drug Approval Package: Ajovy (fremanezumab-vfrm) injection, Summary Review. Application Number 761089. September 14, 2018. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/761089Orig1s000SumR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761089Orig1s000SumR.pdf).
49. Center for Drug Evaluation and Research. Drugs@FDA: Drug Approval Package: Emgality (galcanezumab-gnlm) injection, Summary Review. Application Number 761063. September 27, 2018. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/761063Orig1s000TOC.cfm](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761063Orig1s000TOC.cfm).
50. Depakote DR (divalproex sodium) tablet [package insert]. North Chicago, IL: Abbvie Inc.; Revised October 2017.
51. *Propranolol hydrochloride tablet [package insert]*. Morgantown, WV: Mylan Pharmaceuticals; Revised November 2017.
52. *Propranolol hydrochloride solution [package insert]*. Eatontown, NJ. May 2017: West Ward Pharmaceuticals Corp.; Revised May 2017
53. *Inderal LA (propranolol hydrochloride) extended-release capsule [package insert]*. Baudette, MN: Ani Pharmaceuticals; Revised May 2018
54. *Timolol maleate tablet [package insert]*. Morgantown, WV: Mylan Pharmaceuticals Inc.; Revised August 2006.
55. Dapakote Sprinkles, delayed-release (divalproex sodium) capsule. North Chicago, IL: Abbvie Inc.; Revised October 2017.
56. *Trokindi XR (topiramate) extended-release capsules [package insert]*. Rockville, MD: Supernus Pharmaceuticals; Revised January 2018
57. *Qudexy XR (topiramate) extended-release capsules [package insert]*. Maple Grove, MN: Upsher-Smith Laboratories, Inc.; Revised March 2017.

58. *Topamax (topiramate) Tablets [package insert]. Gurabo, Puerto Rico: Janssen Ortho LLC; Revised June 2018.*



## Appendix A: Database Searches

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### Table 1. Database Searches

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Cochrane Library for Cochrane Reviews\_ November 16<sup>th</sup> 2018

1. erenumab or galcanezumab or fremanezumab [ 0 Cochrane reviews; 158 trails]
2. migraine and [ 57 Cochrane reviews, 4 published in 2018]

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OvidMedline\_ November 16<sup>th</sup>, 2018

- 1 (erenumab or galcanezumab or fremanezumab).ti,kw,kf,ab. [71]
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## Appendix B

Table 1. Additional FDA-Approved Agents for Migraine Prevention <sup>25,26,30-33,50-58</sup>

<b>GENERIC NAME</b> Formulations	<b>Migraine-related Indication<sup>a</sup></b> Dosage
<b>Anticonvulsants</b>	
<b>DIVALPROEX SODIUM</b> <ul style="list-style-type: none"> <li>- Depakote DR, Oral Tablet: 125 mg, 250 mg, 500 mg; generics available</li> <li>- Depakote ER, Oral Tablet: 250 mg, 500 mg; generics available</li> </ul>	<b>Migraine prophylaxis in adults</b> <ul style="list-style-type: none"> <li>- Depakote ER: Initial: 500 mg daily for 1 week, then up to 1000 mg/ day (effective dosage range 500 mg/d – 1000 mg/d)</li> <li>- Depakote DR: Initiate at 250 mg twice daily; may titrate dose up to a maximum of 1000 mg/day</li> </ul>
<b>TOPIRAMATE</b> <ul style="list-style-type: none"> <li>- Topamax, Oral Tablet: 25 mg, 50 mg, 100 mg, 200 mg generics available</li> <li>- Topamax Sprinkles, Oral Capsule: 15 mg, 25 mg; generics available</li> <li>- Trokendi XR, Oral Capsule, Extended-Release: 25 mg, 50 mg, 100 mg, 200 mg; generics available, except for the 200 mg strength</li> <li>- Qudexy XR, Oral Capsule (sprinkle): 25 mg, 50 mg, 100 mg 150 mg, 200 mg</li> </ul>	<b>Migraine prophylaxis in adults and <u>adolescents</u> ≥12 years old</b> <ul style="list-style-type: none"> <li>- Topamax: Initiate at 25 mg in the evening and titrate up according to labeling to the recommended maintenance dose of 50 mg twice daily</li> <li>- Trokendi XR, Qudexy XR and generic topiramate ER: Initiate at 25 mg daily for 1 week and then increase the daily dose by 25 mg each week until reaching the recommended total daily dose of 100 mg per day.</li> </ul> <p>The dose titration rate should be guided by clinical outcome; long-titration intervals may be needed.</p>
<b>Beta-blockers</b>	
<b>PROPRANOLOL</b> <ul style="list-style-type: none"> <li>- Inderal LA, Oral capsule: 60 mg, 80 mg, 120 mg, 160 mg; generics available</li> <li>- <i>Generic only</i>, Oral tablet: 10 mg, 20 mg, 40 mg, 60 mg, 80 mg</li> <li>Oral solution (strawberry-mint flavor): 20 mg/5mL, 40 mg/5mg</li> </ul>	<b>Migraine prophylaxis</b> (safety and effectiveness has not been established in pediatric patients) <ul style="list-style-type: none"> <li>- Initiate at 80 mg (taken once daily for Inderal LA, and as divided doses for propranolol tablets and solution). The maintenance dose range is 160-240 mg daily. If a satisfactory response is not noted at 4-6 weeks at maximum dosage, discontinue propranolol.</li> </ul>
<b>TIMOLOL MALEATE</b>  <i>Generic only</i> , Oral tablet: 5 mg, 10 mg, 20 mg	<b>Migraine prophylaxis</b> (safety and effectiveness has not been established in pediatric patients) Initiate at 10 mg twice daily. Maintenance dosage range 10 mg once daily to 30 mg in divided doses. If a satisfactory response is not noted at 6-8 weeks at maximum dosage, discontinue timolol.
<b>Botulinumtoxin</b>	
<b>ONABOTULINUMTOXINA</b>  Botox, Injection solution: 100 units, 200 units	<b>Chronic migraine prophylaxis in adults</b> (for headaches ≥15 days/month with and lasting ≥4 hours/day) <ul style="list-style-type: none"> <li>- Recommended total dose is 155 units once every 12 weeks, administered intramuscularly, divided across 7 different sites of head/neck muscles. Each 155 unit dose must be divided and administered bilaterally, into 31 total sites as described in the package insert</li> </ul>

Abbreviations: DR, delayed release; ER, extended release

<sup>a</sup> Products have other approved indications in addition to migraine prophylaxis; refer to package inserts for further product information regarding other indications.