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## OHSU Drug Effectiveness Review Project Summary Report – CGRP Inhibitors

**Date of Review:** May 2019

**End Date of Literature Search:** July 31, 2018

**Current Status of PDL Class:**

See **Appendix 1**.

**Research Questions:**

1. What is the efficacy and effectiveness of calcitonin gene-related peptide (CGRP) inhibitors for preventative treatment of episodic or chronic migraines based on important outcomes (e.g., headache frequency or reduction in number of migraines per month) compared to placebo or other treatments?
2. What adverse events are associated with CGRP inhibitors in the preventative treatment of migraines (e.g., withdrawals due to adverse events or severe adverse events)?
3. Are there certain sub-populations (based on age, gender, ethnicity, or comorbidities) in which certain CGRP inhibitors are more effective or cause less harm for migraine preventative treatment?

**Conclusions:**

- No additional high-quality evidence for this review was identified outside the Drug Effectiveness Review Project (DERP) Summary Report.
- Moderate quality evidence from 3 randomized controlled trials (RCTs) of erenumab and fremanezumab compared to placebo showed a statistically significant decrease in migraine days per month for chronic migraine at 12 weeks (-1.7 days to -2.5 days across 3 RCTs).
- Moderate quality evidence from 9 randomized controlled trials of erenumab, fremanezumab, and galcanezumab compared to placebo showed a statistically significant decrease in migraine days per month for episodic migraine at 12 weeks (-0.9 days to -2.8 days across 9 RCTs).
- Low quality evidence from one randomized controlled trial of eptinezumab compared to placebo showed no statistically significant decrease in migraine days per month at 12 weeks.
- There is inadequate evidence to assess the relative efficacy and safety between different CGRP inhibitors or other treatments.
- There is insufficient evidence regarding the long-term safety of CGRP inhibitors beyond 12 to 24 weeks.
- There is insufficient evidence to determine if there is a difference in various subgroup populations in efficacy or safety for eptinezumab, erenumab, fremanezumab, and galcanezumab.

**Recommendations:**

- No new evidence in the DERP report suggests changes should be made to the preferred drug list (PDL) based on clinical differences between agents.
- No further review or research needed at this time. After review of comparative drug costs in the executive session, make all agents non-preferred.

## Summary of Prior Reviews and Current Policy

- In September 2018, a new class was created for the preventative treatment of chronic and episodic migraines called CGRP antagonists. Erenumab was the first agent evaluated and prior authorization (PA) criteria was implemented. The review found insufficient evidence to compare the safety and efficacy of erenumab to any other U.S. Food and Drug Administration (FDA)-approved prophylaxis agents. Two additional agents, fremanezumab and galcanezumab, have been recently FDA-approved and added to the CGRP antagonist class since the initial review (see **Appendix 1**). One additional agent, eptinezumab, is still under FDA review. There were 7 total claims for CGRP antagonists in first quarter (November 2018 – January 2019) for the Oregon Medicaid Fee-For-Service (FFS) population.
- There are currently no preferred agents within the CGRP antagonist class. PA approval criteria requires documentation of 4 or more migraine days per month, failure of FDA-approved migraine prophylaxis agents from select classes (beta-blockers, anticonvulsants, and tricyclic antidepressants), and specialist consult prescribing (see **Appendix 2**).

## Methods:

The October 2018 drug class report on Calcitonin Gene-Related Peptide Inhibitors for Migraine Prophylaxis by the DERP at the Center for Evidence Based Policy at Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. DERP reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

## Summary Findings:

CGRP Inhibitors are human monoclonal antibodies designed to bind to and block CGRP receptor function.<sup>1</sup> It is theorized that migraine headaches may be prevented via inhibition of CGRP-induced vasodilation.<sup>1</sup> The FDA has approved 3 drugs in this class (erenumab, fremanezumab, and galcanezumab) and one additional drug (eptinezumab) is in development and expected to be approved in 2019 (see **Table 1**).<sup>1</sup>

**Table 1. CGRP Inhibitors included in DERP Report<sup>1</sup>**

| Generic Name | Brand Name | Drug Sponsor | Dose(s)                            | Form                   | Frequency                 | FDA Approval Date       |
|--------------|------------|--------------|------------------------------------|------------------------|---------------------------|-------------------------|
| erenumab     | Aimovig    | Amgen        | 70 mg, 140 mg                      | Subcutaneous injection | Monthly                   | May 17, 2018            |
| fremanezumab | Ajovy      | Teva         | 225 mg, 675 mg, 900 mg             | Subcutaneous injection | Monthly or every 3 months | September 14, 2018      |
| galcanezumab | Emgality   | Eli Lilly    | 120 mg (after initial 240 mg load) | Subcutaneous injection | Monthly                   | September 27, 2018      |
| eptinezumab  | N/A        | Alder        | 100 mg, 300 mg                     | Intravenous infusion   | Every 3 months            | <i>Anticipated 2019</i> |

An analysis of the comparative efficacy and safety of the CGRP antagonists in migraine prevention treatment was completed by DERP in October 2018.<sup>1</sup> A search ending in July 2018 identified thirteen randomized, placebo-controlled trials and 2 systematic reviews eligible for inclusion.<sup>1</sup> Narrative reviews and studies not published in English were excluded.<sup>1</sup> The methodological quality of all 13 manufacturer-funded studies were rated as fair due to risk of bias from widespread

manufacturer participation in the study design, protocol, analysis, and synthesis of the document.<sup>1</sup> The DERP review evaluated evidence for the CGRP inhibitors based on effectiveness for chronic migraine prophylaxis, episodic migraine prophylaxis, safety, and use in special populations.<sup>1</sup>

Three studies were identified with evidence for erenumab and fremanezumab use in chronic migraine preventative treatment.<sup>1</sup> Chronic migraine was defined as 15 or more days of headaches per month, for at least 3 months, and with migraine features at least 8 days per month.<sup>1</sup> Ten studies were found with evidence for eptinezumab, erenumab, fremanezumab, and galcanezumab use in episodic migraine prophylaxis.<sup>1</sup> Episodic migraine was defined as any migraine not considered chronic which typically included 4 to 14 migraine days per month.<sup>1</sup> The primary effectiveness outcomes addressed in the studies were changes in migraine or headache events per month from baseline.<sup>1</sup> Medication use days, functional ability, quality of life, adverse events, and withdrawals/discontinuations due to adverse events were mostly reported as secondary outcomes of interest.<sup>1</sup> Many of the secondary outcome measures were based on scores from assessment scales where clinical significance of the treatment effect was difficult to establish.<sup>1</sup>

The CGRP inhibitor DERP summary report did not provide any direct comparative efficacy between eptinezumab, erenumab, fremanezumab, and galcanezumab.<sup>1</sup> An ICER network meta-analysis conducted from studies for common drugs used in preventative therapies for chronic and episodic migraine was included in the report.<sup>1</sup> However, since the network meta-analysis is comprised of indirect comparisons, the summary of this DERP report will focus only on direct evidence of CGRP inhibitors in clinical trials. A systematic review by the Canadian Agency for Drugs and Technologies in Health (CADTH) on monoclonal antibodies in migraine prevention was identified, but will not be addressed in this summary due to its poor methodological quality as reported by the DERP authors.<sup>1</sup> Long-term safety outcomes were not reported for any of the CGRP inhibitors.<sup>1</sup> Fifteen unpublished studies were identified that may provide additional efficacy evidence of up to 24 weeks and safety data up to 1.5 years.<sup>1</sup>

The overall treatment effect magnitude for CGRP inhibitors was minimal as most studies reported an average reduction of 0.9 to 2.8 in migraine days compared to placebo.<sup>1</sup> Slightly larger treatment effects were noted among participants with chronic migraine compared to episodic migraine.<sup>1</sup> The clinical significance of the treatment effect size was unclear.<sup>1</sup>

### **CGRP Inhibitors for Chronic Migraine Prophylaxis**

For chronic migraine prophylaxis, there was moderate quality evidence that select CGRP inhibitors were effective in reduction of migraine days, headache hours, and headache days per month.<sup>1</sup> Overall compared to placebo, erenumab and fremanezumab resulted in a statistically significant decrease in migraine days per month at 12 weeks; the difference from a placebo ranged from -1.7 days to -2.5 days across 3 randomized controlled trials (RCTs).<sup>1</sup> Trial summaries for the individual drugs and their primary outcome measures are presented below.

#### ***Erenumab***

One multicenter, fair quality, phase 2 study (N=667) evaluated erenumab 70 mg and 140 mg versus placebo over 12 weeks.<sup>1</sup> The study enrolled adults between 18 and 65 years of age with a history of chronic migraine in the previous 3 months and during the 4-week run in phase.<sup>1</sup> Concurrent migraine prevention drugs were prohibited in 2 months prior to run-in and during the treatment phase.<sup>1</sup> Acute migraine treatment medications were allowed throughout the study.<sup>1</sup> The primary study endpoint of mean change in migraine days per month from baseline were similar for both active treatment groups (-2.5 [95% CI, -3.5 to -1.4]) compared to the placebo group.<sup>1</sup>

### ***Fremanezumab***

Two studies rated as fair methodological quality evaluated fremanezumab at varying doses and frequencies versus placebo.<sup>1</sup> One multicenter, U.S.-based, phase 2b RCT (N= 264) compared monthly doses of fremanezumab 225 mg and 900 mg versus placebo.<sup>1</sup> A separate phase 3 RCT (N=1,130) conducted in North America and Europe compared fremanezumab 225 mg monthly and 675 mg quarterly to placebo.<sup>1</sup> Patient demographics were similar for both studies consisting of at least 85% females with a mean age of roughly 40 years old.<sup>1</sup> Both studies used 12-weeks of active treatment and allowed up to 2 preventative migraine drugs or devices if use was stable for 2 months prior to 4-week run-in period.<sup>1</sup> The phase 2b study reported statistically significant decreases for primary efficacy endpoints in headache hours per month from baseline for fremanezumab versus placebo [225 mg: -22.7 (-44.3 to -1.2); 900 mg: -30.4 (-51.9 to -9.0)].<sup>1</sup> The phase 3 study also reported statistically significant decreases for its primary efficacy endpoint of headache days per month from baseline for active drug versus placebo [225 mg: -2.1 ± 0.3 (P < .001); 675 mg: -1.8 (P < .001)].<sup>1,2</sup>

### **CGRP Inhibitors for Episodic Migraine Prophylaxis**

For episodic migraine, there was moderate quality evidence that, compared to placebo, erenumab, fremanezumab, and galcanezumab resulted in a statistically significant decrease in migraine days per month at 12 weeks and up to 24 weeks in some studies; the difference from a placebo ranged from -0.9 to -2.8 days per month across 9 RCTs.<sup>1</sup> There was low quality evidence from one RCT that, compared to placebo, eptinezumab resulted in no statistically significant difference in migraine days per month at 12 weeks.<sup>1</sup> Trial summaries for the individual drugs and their primary outcome measures are presented below.

### ***Erenumab***

Two phase 3 RCTs (N=577; N=955) and 1 phase 2 RCT (N=267) evaluated erenumab at 70 mg and 140 mg monthly doses versus placebo.<sup>1</sup> All studies were conducted in multiple study sites in North America and Europe with a 4-week run-in phase and a 12-week or 24-week double-blind active treatment phase.<sup>1</sup> Both phase 3 trials allowed concomitant use of one preventative migraine treatment if the therapy was stable prior to enrollment in the study.<sup>1</sup> Each of the 3 studies reported statistically significant decreases in the primary efficacy endpoint (mean change in monthly migraine days from baseline) for active drug compared to placebo (-1.0 to -1.4 days for 70-mg and -1.9 days (95% CI, -2.3 to -1.4) for 140-mg).<sup>1</sup> Study authors reported many secondary outcomes with regards to changes in quality of life scales which yielded mixed results and variable statistical significance.<sup>1</sup>

### ***Fremanezumab***

One phase 2b RCT (N=297) and one phase 3, RCT (N=875) evaluated fremanezumab 225 mg and 675 mg versus placebo.<sup>1</sup> All doses were administered monthly except for the phase 3 trial which evaluated fremanezumab 675 mg quarterly.<sup>1</sup> Both studies were conducted at multiple sites in 9 countries with a 4-week run-in phase and 12-week double-blind active treatment phase.<sup>1</sup> Participants in both studies allowed concomitant use of one migraine preventive treatment if use was stable prior to enrollment.<sup>1</sup> Both studies reported statistically significant decreases in the primary efficacy endpoint (mean change in monthly migraine days from baseline).<sup>1</sup> The mean difference from the placebo ranged from -1.3 days to -2.8 days across doses.<sup>1</sup>

### ***Galcanezumab***

Four double-blind studies evaluated galcanezumab versus placebo.<sup>1</sup> One phase 2 RCT (N=218) and one phase 2b RCT (N=274) were conducted at multiple U.S. sites.<sup>1</sup> Two studies were phase 3 RCTs (N=862; N=915) conducted at North American sites, one of which also included Europe, South America, and Asia.<sup>1</sup> In the phase 2 trials, galcanezumab doses ranged from 150 mg to 300 mg every 2 weeks or monthly over 3 months.<sup>1</sup> Both phase 3 trials evaluated galcanezumab 120 mg and 240 mg monthly over 6 months.<sup>1</sup> None of the galcanezumab studies allowed concomitant migraine prophylaxis treatment.<sup>1</sup> The studies used the mean change in monthly migraine days from baseline as the primary efficacy endpoint.<sup>1</sup> Compared to placebo, all 4 studies reported statistically significant decreases in migraine days per month which ranged from -0.9 days to -2.0 days across doses, although one study reported results with a 90% confidence interval.<sup>1</sup>

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### **Eptinezumab**

One phase 2 RCT (N=174) evaluated eptinezumab compared to placebo.<sup>1</sup> The study was conducted multiple sites in the U.S. and compared a single 1000 mg intravenous dose of eptinezumab to placebo.<sup>1</sup> No concomitant preventive migraine medication was allowed within 3 months prior to or during the study period.<sup>1</sup> The primary efficacy endpoint was mean change in monthly migraine days from baseline at 5 to 8 weeks.<sup>1</sup> The study authors reported the mean difference compared to placebo to be -1.0 day (95% CI, -2.0 to 0.1) and reported this result as statistically significant (P = .03) using a one-tailed significance test.<sup>1</sup> With data provided in the study, DERP authors calculated the confidence intervals to be -2.0 to 0.04 and the associated P value as 0.06 with a two-tailed t-test.<sup>1</sup> The authors did not observe any significant difference compared to a placebo in monthly migraine days at 12 weeks.<sup>1</sup> The imprecise estimates and small study size limited the author's ability to evaluate efficacy outcomes.<sup>1</sup>

### **CGRP Inhibitor Safety**

Serious adverse events, discontinuations due to adverse events, and all-cause adverse event frequency in active treatment groups were similar in frequency compared to placebo at 12 to 24 weeks across all drugs and doses.<sup>1</sup> Treatment-related liver injury was uncommon and was similar between active treatment and placebo groups.<sup>1</sup> However, the evidence for adverse event outcomes was rated as very low quality for all drugs because of study limitations from the risk of bias due to manufacturer involvement and very serious concerns for imprecision.<sup>1</sup> Long-term safety data for the CGRP inhibitors beyond 24 weeks were not available for evaluation.<sup>1</sup>

### **CGRP Inhibitor Safety and Effectiveness in Sub-populations**

There were few CGRP inhibitor studies that reported findings among sub-populations except for fremanezumab which no reported differences in safety and efficacy among participants with or without concomitant preventative medication.<sup>1</sup> Patients with clinically significant psychiatric or medical conditions including pregnancy were excluded in most studies.<sup>1</sup> Most studies failed to report race and ethnicity information.<sup>1</sup>

### **References:**

1. Kahwati LC, Gartlehner G, Clark R, Patel S, Lazur B, Harrod C. Calcitonin gene-related peptide inhibitors for migraine prophylaxis: a systematic review. Portland, OR: Center for Evidence-based Policy, Oregon Health & Science University; 2018.
2. Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. *N Engl J Med*. 2017;377(22):2113-2122. doi: <https://dx.doi.org/10.1056/NEJMoa1709038>.

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**Appendix 1: Current Preferred Drug List**

| <b><u>Generic</u></b> | <b><u>Brand</u></b>           | <b><u>Form</u></b> |
|-----------------------|-------------------------------|--------------------|
| erenumab-aooe         | AIMOVIG AUTOINJECTOR          | AUTO INJCT         |
| erenumab-aooe         | AIMOVIG AUTOINJECTOR (2 PACK) | AUTO INJCT         |
| fremanezumab-vfrm     | AJOVY                         | SYRINGE            |
| galcanezumab-gnlm     | EMGALITY                      | PEN INJCTR         |

## 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 6 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<br>_____<br>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?<br><br>OR<br><br>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<br>_____<br>_____<br><br>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<br>Approve for up to 6 months (e.g., minimum 2 doses for treatment given every 3 months) | <b>No:</b> Pass to RPh.<br>Deny; medical appropriateness |
|---|--|--|

*P&T/DUR Review: 5/19; 9/18 (DE)  
Implementation: 11/1/2018*