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OHSU Drug Effectiveness Review Project (DERP) Summary Report – CGRP Inhibitors

Date of Review: June 2023

Date of Last Review: October 2021
End Date of DERP Literature Search: November 2022

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- This document is a summary of a research report from the Oregon Health and Science University Drug Effectiveness Review Project (DERP). They studied a group of medicines called calcitonin gene-related peptide (CGRP) inhibitors approved in the United States to treat migraine headaches.
- A migraine headache is a moderate to severe throbbing pain that is usually on one side of the head. A migraine headache usually gets worse with light, physical activity, noises, or smells and often causes the affected person to have nausea or vomiting.
- CGRP inhibitor medicines are used to either prevent migraines or to treat a migraine as it happens. There are 8 CGRP inhibitors approved by the Food and Drug Administration (FDA) for migraine treatment in adults: atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant, ubrogepant, and zavegepant. CGRP inhibitors come in different forms. Some are made to be long acting and given by injection into the skin or into the veins. Other forms may be shorter acting and taken by mouth. Some are used to treat a migraine headache, while others are used to prevent or decrease how often the headaches happen.
- The DERP found that at 12 weeks, most CGRP inhibitors (eptinezumab, erenumab, Fremanezumab, galcanezumab, and sometimes atogepant or rimegepant) helped reduce the number of migraines per month by about 2 days and improved the quality of life in people with regular migraines compared to no use of this medicine.
- DERP also found that certain CGRP inhibitors (eptinezumab, rimegepant, ubrogepant, and zavegepant) helped stop migraine pain and improved ability to do daily living tasks within 2 hours of taking the medicine.
- This report did not find that people taking CGRP inhibitor medicines had many harmful side-effects, but it is not clear how safe and helpful these medicines are if used often in a short time period or for longer than 12 to 16 weeks.
- The Drug Use Research and Management (DURM) group recommends no changes to our current policy for the use of CGRP inhibitor medicines.

Research Questions:

1. What is the new comparative evidence for efficacy and effectiveness for calcitonin gene-related peptide (CGRP) inhibitors for preventative and acute migraine treatment for the outcomes of headache frequency, reduction in the number of migraines, and freedom from pain?
2. What is the evidence for safety associated with CGRP inhibitors when used for the prevention of migraines and acute migraine treatment (e.g. withdrawals due to adverse events or severe adverse events)?

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3. Are there subpopulations in which CGRP inhibitors would be more effective or cause less harm in the treatment of acute migraines or migraine prevention?

Conclusions:

- The evidence included in this review is based on findings from the 2023 Drug Effectiveness Review Project (DERP) report on CGRP inhibitors.[1] Drugs included in the review are atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant, ubrogepant, and zavegepant (**Table 1**).[1] For migraine prevention, the magnitude of treatment effect of CGRP inhibitors was modest among all studies with approximately 0.4 to 3.7 days reduction compared to placebo.[1] Of the studies that evaluated headache severity with the 6-item headache impact test (HIT-6), 15 out of 17 trials reported reductions of 1.9 points or more (higher scores indicate greater impact on quality of life [QoL]; minimum clinically important difference [MCID] 1.5 points).[1]

*Chronic Migraine Prevention (**Table 2**)*

- There is moderate quality of evidence that the use of eptinezumab, erenumab, fremanezumab and galcanezumab reduce the number of migraine days per month (decrease of 1.7 to 2.7 days a month) at 12 weeks compared to placebo. [1]
- QoL was improved, compared to placebo, with the use of eptinezumab, erenumab, and fremanezumab at 12 weeks as measured by the HIT-6 with a difference of 1.1 to 5.6 points, which suggests a variable clinical benefit (4 randomized controlled trials (RCTs); moderate quality of evidence); galcanezumab was more effective than placebo at improvements in QoL based on the Migraine-specific quality of life score (MSQL) measure (moderate quality of evidence). The clinical significance of QoL improvements based on the MSQL are unclear.[1]

*Episodic Migraine Prevention (**Table 3**)*

- The number of migraine days per month were reduced with atogepant, eptinezumab, erenumab, fremanezumab and galcanezumab compared to placebo, with a difference ranging from -0.4 to -3.0 days (18 RCTs; moderate quality of evidence).[1]
- Erenumab, fremanezumab, and galcanezumab were more effective than placebo at improving quality of life based on moderate quality of evidence.[1]

*Chronic or Episodic Migraine [Mixed Populations of Both Types] (**Table 4**)*

- There is moderate quality of evidence that the use of eptinezumab, erenumab, fremanezumab, galcanezumab and rimegepant reduce the number of migraine days per month (range 0.8 to 3.7 fewer days per month) for chronic or episodic migraine at 12 to 24 weeks compared to placebo (5 RCTs).[1]
- There was a statistically significant decrease in migraine days per month for erenumab therapy compared to topiramate (decrease of 1.8 days, 95% confidence interval [CI], -1.3 to -2.4; moderate quality of evidence); erenumab treatment was also associated with larger QoL improvements (moderate quality of evidence).[1]
- There was moderate quality of evidence that eptinezumab and fremanezumab were more effective at improvement of functioning as measured by the HIT-6 (range of effects in mean difference 3.0 points to 5.4 points) compared to placebo which is suggestive of clinical benefit.[1]

*Acute Migraine Treatment **(Table 5**)*

- For the outcome of proportion of patients with freedom from pain at 2 hours, rimegepant and ubrogepant were more effective than placebo (difference range of 7.4% to 16.6%) based on moderate quality of evidence.[1]
- Zavegepant is the newest CGRP inhibitor agent recently FDA approved for acute migraine treatment.[1] One phase 3 RCT reported that at 2 hours post-dose, zavegepant 10 mg and 20 mg were more effective than placebo in proportion of participants achieving freedom from pain (risk difference [RD] 7% and 7.7%, respectively) and freedom from most bothersome symptom (RD 8.3% and 8.9%, respectively) based on low quality evidence.[1] There was no significant difference in these outcomes for zavegepant 5 mg.[1]

Cluster Headache Prevention

- Compared to placebo, there was low quality evidence that galcanezumab was more effective in the short term (1 to 3 weeks) prevention of cluster headache (2.2 to 3.5 fewer attacks) but no difference in cluster headache prevention at weeks 8 to 12.[1]

Acute Cluster Headache Treatment

- No studies were identified with CGRP inhibitors used for acute cluster headache treatment.[1]

Adverse Effects from CGRP Inhibitors

- There was only low quality of evidence available for the comparison of adverse events (AEs) between CGRP inhibitors and placebo for all treatment studied.[1] Adverse events (e.g. constipation, injection site pain, infection), severe adverse events, and discontinuations due to adverse events were rare and similar to placebo for the majority of CGRP inhibitors. [1] Many of the included studies only evaluated treatment of one or few attacks, which may limit the capturing of harms data.

Subgroup Differences in Efficacy and Adverse Events

- There is insufficient evidence for the use of CGRP inhibitors in different subgroups or evidence of benefit beyond 24 weeks. [1]
- There is insufficient evidence of comparative differences between CGRP inhibitors or their use in combination with any other agent.

Recommendations:

- Update prior authorization criteria (**Appendix 2**).
- After clinical review no changes to the preferred drug list (PDL) are recommended.
- After evaluation of costs in executive session, no changes were made to the PDL.

Summary of Prior Reviews and Current Policy

- A review in October 2021 updated PA requirements for all therapies in the CGRP inhibitor PDL class. Current PA requires documentation of at least 4 migraines per month, failure of FDA approved migraine prophylactic therapies (beta-blockers, anticonvulsants, and tricyclic antidepressants) and a specialist consult for approval. Erenumab and fremanezumab are currently preferred therapy options in the CGRP inhibitor PDL class.
- There were fewer than 100 claims for CGRP inhibitors during first quarter of 2023 for Oregon Health Plan (OHP) Fee-for-Service (FFS) population.

Methods:

The January 2023 drug class report on Calcitonin Gene-Related Peptide Inhibitors for Migraine Prevention and Treatment and for Cluster Headache Prevention by the Drug Effectiveness Review Project (DERP) at the Center for Evidence Based Policy at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.[1] 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 migraine therapies used to block CRGP, which is thought to play a role in migraine prevention, acute migraine treatment and cluster headache.[1] There are 8 CGRP inhibitors approved by the Food and Drug Administration (FDA) for migraine treatment in adults (Table 1).[1] CGRP inhibitors come in various formulations and may be administered subcutaneously [SC], intravenously [IV], or orally.[1] Some agents are monoclonal antibodies that target the CGRP

receptor (erenumab) or CGRP ligand (eptinezumab, fremanezumab, and galcanezumab), while others are small molecule agents that inhibit the CGRP receptor (atogepant, rimegepant, ubrogepant, and zavegepant).[1]

Table 1. CGRP Inhibitors Included in DERP Report[1]

Drug	Dose	Approval Date	Approved Indication	Number of RCTs Included
Atogepant QUILIPTA	10 mg, 30 mg, or 60 mg orally once daily	September 2021	Migraine Prevention	2
Eptinezumab VYEPTI	100 mg or 300 mg IV every 3 months	February 2020	Migraine Prevention	6
Erenumab AIMOVIG	70 mg or 140 mg SC every month	May 2018	Migraine Prevention	9
Fremanezumab AJOVY	225 mg SC monthly or 675 mg SC every 3 months	September 2018	Migraine Prevention	7
Galcanezumab EMGALITY	Migraine: 120 mg SC every month Cluster: 300 mg SC every month	September 2018 and June 2019	Migraine Prevention Cluster Headache Prevention	9
Rimegepant NURTEC	75 mg orally as needed for acute migraine attack	February 2020; May 2021 (new indication)	Acute Migraine Treatment Migraine Prevention	3
Ubrogepant UBRELVY	50 mg or 100 mg once orally for acute migraine attack, may repeat dose	December 2019	Acute Migraine Treatment	4
Zavegepant ZAVZPRET	10 mg (one spray) intranasally per 24 hours*	March 2023*	Acute Migraine Treatment	1

*=FDA labeling; product availability anticipated July 2023.

The purpose of this DERP report is to update evidence for the use of CGRP inhibitors since the previous published report in April 2020.[1] Literature was searched through November 8, 2022.[1] Main outcomes of interest were migraine or headache days per month or pain relief for acute migraine, functional outcomes, QoL, SAEs, and discontinuations due to AEs.[1] There is no established clinically important difference for headache day reduction in migraine prevention. Quality of life assessment tools used for the determination of headache severity were the HIT-6, MSQL and Migraine Disability Assessment (MIDAS).[1] The HIT-6 consists of 6 items (pain, social functioning, role functioning, vitality, cognitive functioning, and psychological distress) that are ranked from “never”, “rarely”, “sometime”, “very often” or “always”.[1,2] Higher HIT-6 scores are related to a greater impact on quality of life with a range of 36-78 points.[1,2] A score of 60 or more is considered severe impact on QoL.[2] A change of 1.5 units has been suggested as the MCID for the HIT-6 instrument based on clinically relevant changes in primary care populations with migraines.[1,2] The MSQL is a 14-item questionnaire used to determine migraine disability with scores ranging from 0-100, higher scores indicate a higher quality of life.[1,2] A 6-point scale is used to rate disability from “none of the time” to “all of the time”, which are assigned a score of 1-6.[1,2]

The MIDAS test is used to quantify headache disability based on a 7-item questionnaire.[1,2] The score is based on activity limitations ranging from little or no disability (0-5) to severe disability (21 or more).[1,2] For the MIDAS, as with many of the migraine quality of life assessments, the scores are not well defined and the MCID has not been determined. A total of 15 new RCTs were identified for a total trial inclusion of 42.[1] All trials were placebo-controlled and there was insufficient evidence for direct comparison of different CGRP inhibitors.[1] One RCT compared rimegepant with sumatriptan for acute migraine treatment and 1 RCT compared erenumab with topiramate for the prevention of chronic or episodic migraine.[1] The quality of studies was considered moderate except for 1 poor quality trial.[1]

Chronic Migraine Prevention

Eptinezumab, erenumab, fremanezumab, and galcanezumab are used for the prevention of chronic migraine. Erenumab and galcanezumab were studied in one randomized controlled trial, eptinezumab in 2 trials, and fremanezumab in 3 trials.[1] Patients in the studies had a mean of 14.1 days to 19.6 days migraine days per month.[1] Outcomes with moderate evidence are presented in Table 2. All therapies were found to be more effective than placebo for the outcomes of number of migraine days per month, for the percent of patients with a 50% reduction in migraine days, and days with acute headache medication use per month.[1] Eptinezumab, erenumab, and fremanezumab were more effective at improving functioning at 12 weeks compared to placebo as measured by the HIT-6 (range 1.1 to 5.6 points).[1] The evidence for serious adverse events and discontinuations due to adverse events were associated with low or very low quality of evidence.[1] Trial summaries for the individual drugs and their outcome measures are presented below.

Table 2. CGRP Inhibitors for Chronic Migraine Prevention[1]

Drug	**Results** (Mean difference from placebo; 95% CI; all reported statistically significant results based on an alpha equal to .05) **Outcome:** Migraine days per month	**Number of Trials; Assessment Timing**	**Quality of Evidence**
Eptinezumab	*Dodick et al* 100 mg: -2.1 (-3.8 to -0.4) 300 mg: -2.7 (-4.4 to -0.9) *Lipton et al* 100 mg: -2.0 (-2.9 to -1.2) 300 mg: -2.6 (-3.4 to -1.7)	2 RCTs; Weeks 1 to 12 Weeks 1 to 12	Moderate
Erenumab	70-mg and 140-mg doses: -2.5 (-3.5 to -1.4)	1 RCT; Weeks 9 to 12	
Fremanezumab	*Bigal et al** 225 mg (monthly): -1.8 (-3.5 to -0.14) 900 mg (quarterly): -2.0 (-3.7 to -0.26) *Sakai et al* 225 mg (monthly): -1.7 (-2.5 to -0.8) 675 mg (quarterly): -1.7 (-2.6 to -0.8)	3 RCTs; Weeks 9 to 12 Monthly Quarterly	

	Silberstein et al 225 mg (monthly): -1.8 (No CI reported) 675 mg (quarterly): -1.7 (No CI reported)	Weeks 9 to 12	
Galcanezumab	Range: -2.1 to -1.9	1 RCT; Weeks 4 to 12	
	Outcome: Percentage of patients with at least 50% reduction in number of migraine days per month		
Eptinezumab	*Dodick et al* 100 mg: 14.6%/NNT 7 (No CI reported) 300 mg: 16.5%/NNT 7 (No CI reported) *Lipton et al* 100 mg: 18.2% (11.1 to 25.4)/ NNT 6 300 mg: 22.1% (14.9 to 29.2)/ NNT 5	2 RCTs Weeks 1 to 12 Weeks 1 to 12	Moderate
Erenumab	70-mg: RR 1.70 (1.29 to 2.23) 140-mg: RR 1.75 (1.34 to 2.30)	1 RCT 12 weeks	
Fremanezumab	*Sakai et al* 225 mg (monthly): 15.9% (7.8 to 24.0)/NNT 7 675 mg (quarterly): 15.9% (7.9 to 24.0)/NNT 7 *Silberstein et al** 225 mg: RD 22.7% (16.4 to 29.1)/NNT 5 675 mg: 19.5% (13.3 to 25.8)/NNT 6	2 RCTs Weeks 4 to 16 Weeks 9 to 12	
Galcanezumab	120 mg: 28%/NNT 4 (No CI reported) 240 mg: 28%/NNT 4 (No CI reported)	1 RCT Weeks 4 to 12	
	Outcome: Days with acute migraine medication use per month		
Erenumab	70 mg: -1.9 (-2.6 to -1.1) 140 mg: -2.6 (95% CI, -3.3 to -1.8)	1 RCT Weeks 9 to 12	Moderate
Fremanezumab	*Bigal et al** 225 mg: -2.2 (-4.0 to 0.3) 900 mg: -2.0 (-3.9 to -0.20) *Silberstein et al** 225 mg: (monthly): -2.3 (No CI reported) 675 mg (quarterly): -1.8 (No CI reported)	3 RCTs Weeks 9 to 12 Weeks 9 to 12	Moderate

	Sakai et al 225 mg (monthly): -1.3 (-2.2 to -0.4) 675 mg (quarterly): -1.4 (-2.3 to -0.6)	Weeks 4 to 16	
Galcanezumab	*Detke et al* 120 mg: -2.5 days (-3.3 to -1.8) 240 mg: -2.0 days (-2.8 to -1.3)	1 RCT Weeks 4 to 12	Moderate
	Outcome: Mean point change in HIT-6		
Eptinezumab	100 mg: -1.7 (No CI reported) 300 mg: -4.2 (-6.3 to -2.1) -2.9 (-3.9 to -1.8)	1 RCT Week 12	Moderate
Erenumab	70 mg: -5.6 (-6.5 to -4.6) 140 mg: -3.1 (-3.9 to -2.3)	1 RCT Week 12	
Fremanezumab	*Sakai et al* 225 mg (monthly): -1.6 (-2.9 to -0.2) 675 mg (quarterly): -1.5 (-2.9 to -0.2) *Silberstein et al** 225 mg: (monthly): -2.4 (No CI reported) 675 mg (quarterly): -1.9 (No CI reported)	2 RCTs Weeks 4 to 16 Week 12	
	Outcome: Mean point change in MSQL		
Galcanezumab	120 mg: -5.1 (-8.0 to -2.1) 240 mg: -6.3 (-9.6 to -3.0)	1 RCT Weeks 4 to 12	Moderate

*=Patients in the 225-mg group received 675-mg of fremanezumab at baseline and 225-mg of fremanezumab at weeks 4 and 8
Abbreviations: CI = confidence interval; HIT-6 = headache impact test; MSQL = Migraine-specific quality of life score; NNT = number needed to treat; RCT = randomized controlled trial

Episodic Migraine Prevention Atogepant, eptinezumab, erenumab, fremanezumab, and galcanezumab were studied for episodic migraine prevention.[1] Patients had a history of 6.6 to 11.3 migraine headache days per month at baseline.[1] All therapies were more effective than placebo for the reduction in mean number of headache days per month by 1 to 2 days (range 0.4 days to 3 days).[1] All 5 drugs improved QoL/functional measures although there were different instruments employed (e.g. HIT-6, MIDAS, MSQL) and variable quality of evidence (moderate quality evidence for erenumab, fremanezumab, and galcanezumab; low quality evidence for atogepant and eptinezumab).[1] The evidence for serious adverse events and discontinuations due to adverse events were similar to placebo (very low quality of evidence).[1] Trial summaries for the individual drugs and their primary outcome measures with at least moderate quality evidence are presented in **Table 3**.

Table 3. CGRP Inhibitors for Episodic Migraine Prevention[1]

Drug	**Results** (Mean difference from placebo; 95% CI; all reported statistically significant results based on an alpha equal to .05) **Outcome:** Migraine days per month	**Number of Trials; Assessment Timing**	**Quality of Evidence**
Atogepant	*Ailani et al* 10-mg: -1.2 (-1.8 to -0.6) 30-mg: -1.4 (-1.9 to -0.8) 60-mg: -1.7 (-2.3 to -1.2) *Goadsby et al* 10-mg: -1.2 (-1.9 to -0.4) 30-mg: -0.9 (-1.6 to -0.3) 60-mg: -0.7 (-1.4 to -0.1)	2 RCTs Week 12 Week 12	Moderate
Eptinezumab	*Ashina et al.* 100-mg: -0.7 (-1.3 to -0.1) 300-mg: -1.1 (-1.7 to -0.5) *Dodick et al.* 1,000-mg: -1.0 (-2.0 to 0.1)	2 RCTs Week 12 Weeks 5 to 8	
Erenumab	*Dodick et al; Kawata et al.* 70-mg: -1.0 (-1.6 to -0.5) *Goadsby et al.; Buse et al.; Kawata et al.* 70-mg: -1.4 (-1.9 to -0.9) 140-mg: -1.9 (-2.3 to -1.4) *Sakai et al.* 70-mg: -2.3 (-3.0 to -1.6) 140-mg: -1.9 (-2.6 to -1.2) *Sun et al.* 70-mg: -1.1 (-2.1 to -0.2) *Wang et al.* 70-mg: -1.1 (-1.8 to -0.4)	6 RCTs Weeks 9 to 12 Months 4 to 6 Months 4 to 6 Weeks 9 to 12 Week 12	

	140-mg: -1.7 (-2.5 to -0.9)		
Fremanezumab	*Bigal et al.* 225-mg: -2.8 (-4.1 to -1.6) 675-mg: -2.6 (-3.9 to -1.4) *Dodick et al.* 225-mg: -1.5 (-2.0 to -0.9) 675-mg: -1.3 (-1.8 to -0.7) *Sakai et al.* 225-mg: -3.0 (-3.7 to -2.2) 675-mg: -3.0 (-3.8 to -2.2)	3 RCTs Weeks 9 to 12 Weeks 9 to 12 Week 12	
Galcanezumab	*Dodick et al.* 1.2 (90% CI, -1.9 to -0.6) *Skljarevski et al.; Oakes et al.; Ayer et al.* 120-mg: -0.9 (No CI reported) 300-mg: -0.9 (No CI reported) *Skljarevski et al* 120 mg: -2.0 (-2.6 to -1.5) 240-mg: -1.9 (-2.4 to -1.4) *Stauffer et al.* 120-mg: -1.9 (-2.5 to -1.4) 240-mg: -1.8 (-2.3 to -1.2)	5 RCTs Weeks 9 to 12 Weeks 9 to 12 6 months 6 months	
	Outcome: Percentage patients with at least 50% reduction in number of migraine days per month		
Eptinezumab	*Ashina et al.* 100 mg: RD = 12.4 (3.2 to 21.5)/NNT 9 300 mg: 18.9 (9.8 to 28.0)/NNT 6	2 RCTs Week 12	Moderate
Erenumab	*Reuter et al.* 140-mg: OR, 2.7 (1.4 to 5.2) *Sakai et al.* 70 mg: OR = 5.6 (2.6 to 12.1) 140 mg: OR = 4.7 (2.2 to 10.0) *Goadsby et al.*	6 RCTs Weeks 9 to 12 Weeks 9 to 12	

	70 mg: OR = 2.1 (1.5 to 2.9) 140 mg: OR = 2.8 (2.0 to 3.9) <u>*Sun et al*</u> 70 mg: OR = 2.0 (1.2 to 3.4) <u>*Wang et al.*</u> 70 mg: OR = 1.5 (1.1 to 2.1) 140 mg: OR = 2.2 (1.6 to 3.2) <u>*Dodick et al.*</u> 70 mg: OR = 1.59 (1.12 to 2.27)	Months 4 to 6 Weeks 9 to 12 Week 12 Weeks 9 to 12	
Fremanezumab	*Bigal et al.* 225 mg: RD = 21.2% (7.6 to 34.7)/NNT 5 675 mg: RD = 22.7% (9.2 to 36.1)/NNT 5 <u>*Dodick et al.*</u> 225 mg: RD = 19.8% (12.0 to 27.6)/NNT 6 675 mg: RD = 16.5% (8.9 to 24.1)/NNT 7 <u>*Sakai et al*</u> 225 mg monthly: RD = 30.1% (19.6 to 40.6)/NNT 4 675 mg quarterly: RD = 34.1% (23.4 to 44.7)/NNT 3	Weeks 9 to 12 Weeks 9 to 12 Months 4 to 6	
Galcanezumab	<u>*Dodick et al.*</u> 150 mg (every 2 weeks): RD = 25.2% (12.1 to 38.4)/NNT 4 <u>*Sakai et al.; Shibita et al.*</u> 120 mg: RD = 29.1% (18.6 to 39.7)/NNT 4 240 mg: RD = 27.8% (17.3 to 38.4)/NNT 4 <u>*Skljarevski et al.*</u>	5 RCTs Weeks 9 to 12 Months 1 to 6 Weeks 9 to 12	

	120 mg: RD = 23.3% (15.6 to 31.0)/NNT 5 240 mg: RD = 20.5% (12.7 to 28.3)/NNT 5 *Stauffer et al.* 120 mg: RD = 23.8% (15.8 to 31.8)/NNT 5 240 mg: RD = 22.5% (14.4 to 30.6)/NNT 5	6 months	
	Outcome: Mean point change in HIT-6 from baseline		
Erenumab	*Dodick et al., Reuter et al., Sakai et al., Goadsby et al., Sun et al, Wang et al.* HIT-6 Improvement: Range = -3.0 to -1	6 RCTs Weeks 9 to 12	Moderate
	Outcome: Mean point change in MIDAS/MSQL from baseline		
Fremanezumab	*Bigal et al.* (MIDAS) 225 mg: -14.5 (-26.8 to -2.2) 675 mg: -15.2 (-27.6 to -2.8) *Dodick et al.* (MIDAS) 225 mg: -7.0 (-10.5 to -3.5) 675 mg: -5.4 (-8.9 to -1.9) *Sakai et al.* (MIDAS) 225 mg: -5.2 (-8.1 to -2.3) 675 mg: -5.1 (-8.1 to -2.2)	3 RCTs Weeks 9 to 12 Weeks 9 to 12 Week 12	Moderate
Galcanezumab	*Dodick et al., Sakai et al., Shibata et al., Tatsuoka et al., Skljarevski et al* MIDAS: Range = -9.2 to -3.0 MSQL: Range = -8.8 to -5.8	5 RCTs Months 4 to 6 Months 4 to 6	Moderate

Abbreviations: CI = confidence interval; HIT-6 = headache impact test; MIDAS = Migraine Disability Assessment; MSQL = Migraine-specific quality of life score; NNT = number needed to treat; RCT = randomized controlled trial

Chronic or Episodic Migraine Prevention

For chronic or episodic migraine prevention (study populations included both types and results were not stratified), there was moderate quality of evidence from 5 RCTs that eptinezumab, erenumab, fremanezumab, galcanezumab, and rimegepant were more effective than placebo in reduction of migraine days per month (range 0.8 to 3.7 fewer days per month).[1] Only eptinezumab, erenumab, and fremanezumab were more effective than placebo in outcomes of percentage of participants with at least 50% reduction in migraine days (moderate quality evidence).[1] There was moderate quality evidence that erenumab resulted in a statistically significant decrease in migraine days per month compared with topiramate (MD -1.8 [95% CI, -1.3 to -2.4]; it also was associated with larger improvements in QoL (moderate CoE). About 39% of the topiramate group had at least 1 adverse event leading to treatment discontinuation compared to 11% of those on erenumab which may have resulted in significant attrition bias. Eptinezumab and fremanezumab were more effective than placebo at improvement in function as measured by the HIT-6 (range 3.0 to 5.4 points; moderate quality of evidence).[1] **Table 4** summarizes these findings.

Table 4. CGRP Inhibitors for Chronic or Episodic Migraine Prevention (Mixed Populations)[1]

Drug	**Results** (Mean difference from placebo unless noted; 95% CI; all reported statistically significant results based on an alpha equal to .05)	**Number of Trials; Assessment Timing**	**Quality of Evidence**
	Outcome: Migraine days per month		
Eptinezumab	100-mg: -2.7 (-3.4 to -2.0) 300-mg: -3.2 (-3.9 to -2.5)	1 RCT Weeks 1 to 12	Moderate
Erenumab	70 mg or 140 mg: -1.6 (-2.5 to -0.7)	1 RCT Weeks 16 to 24	Moderate
Fremanezumab	225 mg (monthly): -3.5 (-4.2 to -2.8) 675 mg (quarterly): -3.1 (-3.8 to -2.4)	1 RCT Weeks 1 to 12	Moderate
Galcanezumab	120 mg: -3.1 (-3.9 to -2.3)	1 RCT Weeks 4 to 16	Moderate
Rimegepant	75 mg: -0.8 (-1.5 to -0.2)	1 RCT Weeks 9 to 12	Moderate
	Outcome: Percentage patients with at least 50% reduction in number of migraine days per month		
Eptinezumab	100 mg: 29.1%/NNT 4 300 mg: 36.4%/NNT 3	1 RCT Weeks 1 to 12	Moderate
Erenumab	*Reuter et al* (vs Topiramate) Erenumab: 55% Topiramate: 31% RD = 22%/NNT 5	1 RCT Weeks 16 to 24	Moderate
Fremanezumab	225 mg (monthly) and 675 mg (quarterly): 34%/NNT	1 RCT Weeks 1 to 12	Moderate
	Outcome: Mean Change HIT-6 Score		
Eptinezumab	100 mg: -3.8 (-5.0 to -2.5) 300 mg: -5.4 (-6.7 to -4.2)	1 RCT Weeks 1 to 12	Moderate
Erenumab	70 mg and 140 mg (vs Topiramate):	1 RCT	Moderate

	-3.2 (-4.3 to -2.1)	Weeks 16 to 24	
Fremanezumab	225 mg: -3.8 (-5.0 to -2.7) 675 mg: -3.0 (-4.1 to -1.8)	1 RCT Week 12	Moderate

Abbreviations: CI = confidence interval; HIT-6 = headache impact test; NNT = number needed to treat; RCT = randomized controlled trial

Acute Migraine Treatment

Rimegepant and ubrogepant are two small molecule CGRP inhibitors used for the acute treatment of migraine. A third and the newest CGRP agent, zavegepant, had not yet been FDA approved at the time of the review.[1] Rimegepant and ubrogepant were studied in 3 randomized controlled trials (**Table 5**).[1] There was moderate quality evidence that rimegepant and ubrogepant were more effective than placebo for the outcomes of freedom from pain at 2 hours and freedom from most bothersome symptom at 2 hours.[1]

Zavegepant (Zavzpret®) was approved by the FDA in March 2023 after completion of the DERP report.[1] The efficacy and safety of zavegepant was studied in one phase 2/3, double blind RCT (N=1,581) at multiple sites in the US. The study included mostly females (86%) with a 1-year history of migraine of at least 2 attacks per month where untreated migraines lasted 4 to 72 hours.[1] Patients with history of hemiplegic migraine, unstable medical conditions, opioid use, or recent use of nasal sprays were excluded.[1] Patients were randomized into 4 groups of roughly equal proportions and given either zavegepant 5-mg, 10-mg, 20-mg or placebo.[1] Primary endpoints were freedom from pain or freedom from most bothersome symptoms at 2 hours post-dose.[1] There was low quality evidence that at two hours post-dose, zavegepant 10 mg and 20 mg were more effective than placebo in proportion of participants achieving freedom from pain (RD 7% and 7.7%, respectively) and freedom from most bothersome symptom (RD 8.3% and 8.9%, respectively).[1] Zavegepant 5 mg comparison to placebo did not reach statistical significance for the pre-defined study outcomes.[1]

The new CGRP inhibitor agent zavegepant and those agents with at least moderate quality evidence for acute migraine treatment outcomes are reported in Table 5.

Table 5. CGRP Inhibitors for Acute Migraine Treatment[1]

Drug	**Results*** (Mean difference from placebo unless noted) **Outcome:** Proportion patients with freedom from pain at 2 hours post-dose	**Number of Trials; Assessment Timing**	**Quality of Evidence**
Rimegepant	vs. Placebo *Croop et al* 75 mg: 10.4% (6.5% to 14.2%) /NNT 10 *Lipton et al* 7.6% (3.3% to 11.9%)/NNT 14 *Marcus et al* 16.2% (5.2% to 27.1%)/NNT 7 vs. Sumatriptan *Marcus et al*	3 RCTs; 2 hours all trials 1 RCT N/A	Moderate

	-3.6% (-17.2% to 9.9%) *No statistically significant difference as calculated by DERP authors*		
Ubrogepant	*Dodick et al* 50-mg: 7.4% (2.6% to 12.1%)/NNT 14 100-mg: 9.4% (4.6% to 14.2%)/NNT 11 *Lipton et al* 50-mg: 7.5% (2.6 % to 12.5%)/NNT 14 *Voss et al* 50-mg: 12.0% (2.6 to 21.4)/NNT 9 100-mg: 16.6% (12.4 to 22.4)/NNT 6	3 RCTs; 2 hours all trials	Moderate
Zavegepant	*Croop et al* 5 mg: 4.2% (not statistically significant) 10 mg: 7% (1.6 to 12.5)/NNT 15 20 mg: 7.7% (2.2 to 13.1)/NNT 13	1 RCT; 2 hours	Low
	Outcome: Proportion of patients with freedom from most bothersome symptom at 2 hours post-dose		
Rimegepant	*Croop et al* 75 mg: 8.3% (3.4% to 13.2%)/NNT 13 *Lipton et al* 12.4% (6.9% to 17.9%)/NNT 9	2 RCTs; 2 hours all trials	Moderate
Ubrogepant	*Dodick et al* 50-mg: 10.8% (4.6% to 17.0%)/NNT 10 100-mg: 10.0% (3.9% to 16.1%)/NNT 10 *Lipton et al* 50-mg: 11.5% (5.4% to 17.5%)/NNT 9	2 RCTs; 2 hours all trials	Moderate
Zavegepant	*Croop et al* 5 mg: 5.4% (not statistically significant) 10 mg: 8.3% (1.5 to 15.0)/NNT 13 20 mg: 8.9% (2.2 to 15.6)/ NNT 12	1 RCT; 2 hours	Low

*=95% CI; all reported statistically significant results based on an alpha equal to .05 unless otherwise noted
Abbreviations: CI = confidence interval; NNT = number needed to treat; RCT = randomized controlled trial

Acute Cluster Headache Treatment

There were no new studies identified that assessed the effectiveness of CGRP inhibitors for acute cluster headache prevention since the previous DERP report.[1]

Cluster Headache Prevention

For cluster headache prevention, there was low-quality evidence that galcanezumab is not effective and very low quality of evidence for harms due to the rarity of events.[1] Although galcanezumab resulted in statistically significant reduction in cluster headache attack frequency per week during weeks 1 through 3 compared to placebo (range 2.2 to 3.5 fewer), there was no difference at weeks 8 to 12 (range 0.8 fewer to 1.3 more attacks per week).[1]

Adverse Events from CGRP Inhibitors

The DERP review was unable to determine a relationship between active CGRP treatment and adverse events (e.g. constipation, injection site pain, infection, etc.) due to the infrequent reporting of severe adverse events and discontinuations due to adverse events.[1] The frequency of AEs, SAEs, and discontinuations due to AEs was similar between active treatment groups and placebo for virtually all indications, drugs, and dosages (very low quality of evidence).[1] Erenumab had fewer discontinuations due to AEs compared to topiramate (moderate quality of evidence).[1] No discontinuations due to AEs were reported in trials that compared rimegepant to sumatriptan (very low quality of evidence).[1] Liver injury due to treatment was uncommon with CGRP treatment in studies that reported that outcome.[1]

Subgroup Differences in Efficacy and Adverse Events

There were few studies that reported subgroup findings.[1] Five fremanezumab studies evaluated efficacy among participants who were not taking preventative medications compared to the full study population and reported similar efficacy.[1] There were no studies found for use of CGRP inhibitors in combination with any other agent.

Evidence Limitations

Studies were industry sponsored and evidence was downgraded due manufacturer sponsorship and extensive involvement in the trials themselves.[1] There were no head-to-head trials that directly compared two or more CGRP inhibitors.[1] Many trials were of short duration (12 weeks) preventing long-term evidence for efficacy and harms in a condition that is typically treated chronically as long-term therapy.[1] Only studies of single, acute migraine attacks were assessed, therefore effectiveness and safety of repeated use is unknown.[1] Most studies employed an electronic headache diary during a run-in phase so generalizability to a less selective population was uncertain.[1] Patients who were pregnant or those with clinically significant psychiatric or medical conditions were excluded so the effects in a less selective study population was unknown.[1] Most studies included a high majority of females and did not report information on race and ethnicity.[1]

References:

1. Drug Effectiveness and Review Project (DERP). Calcitonin Gene-Related Peptide Inhibitors for Migraine Prevention and Treatment and for Cluster Headache Prevention. Center for Evidence-based Policy, Oregon Health & Science University; 2023.
2. Institute for Clinical and Economic Review. Calcitonin Gene-Related Peptide (CGRP) Inhibitors as Preventive Treatments for Patients with Episodic or Chronic Migraine: Effectiveness and Value. Final Evidence Report. July 2018. Accessed March 14, 2023. https://icer.org/wp-content/uploads/2020/10/ICER_Migraine_Final_Evidence_Report_070318.pdf

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	Route	PDL
erenumab-aooe	AIMOVIG AUTOINJECTOR	AUTO INJCT	SQ	Y
fremanezumab-vfrm	AJOVY AUTOINJECTOR	AUTO INJCT	SQ	Y
fremanezumab-vfrm	AJOVY SYRINGE	SYRINGE	SQ	Y
atogepant	QULIPTA	TABLET	PO	N
eptinezumab-jjmr	VYEPTI	VIAL	IV	N
galcanezumab-gnlm	EMGALITY PEN	PEN INJCTR	SQ	N
galcanezumab-gnlm	EMGALITY SYRINGE	SYRINGE	SQ	N
galcanezumab-gnlm	EMGALITY SYRINGE	SYRINGE	SQ	N
rimegepant sulfate	NURTEC ODT	TAB RAPDIS	PO	N
ubrogepant	UBRELVY	TABLET	PO	N
zavegepant	ZAVZPRET	SPRAY	NS	N

Appendix 2: Prior Authorization Criteria

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 for migraine prevention, acute migraine treatment and cluster headache prevention (Table 1).

Length of Authorization:

- Initial: Up to 3 months
- Renewal: Up to 6 months

Requires PA:

- All calcitonin gene-related peptide (CGRP) antagonist pharmacy and practitioner administered claims

Covered Alternatives:

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

Table 1. FDA Approved Indications for CGRP antagonists

Drug	FDA Approved Indication
Atogepant	Preventative migraine treatment
Eptinezumab	Preventative migraine treatment
Erenumab	Preventative migraine treatment
Fremanezumab	Preventative migraine treatment
Galcanezumab	Preventative migraine treatment and cluster headache prevention
Rimegepant sulfate	Acute migraine treatment and preventative treatment of episodic migraine
Ubrogepant	Acute migraine treatment
Zavegepant	Acute migraine treatment

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is this an FDA-approved indication (Table 1)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for renewal of a previously approved Fee-For-Service prior authorization of a CGRP antagonist for management of migraine headache?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the medication being prescribed by or in consultation with a neurologist or headache specialist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to # 6
6. Is the request for acute (abortive) migraine treatment AND the patient is an adult (18 years or older)?	**Yes:** Go to #12	**No:** Go to #7
7. Is the request for the prevention of cluster headache AND the patient is an adult (18 years or older)?	**Yes:** Go to #15	**No:** Go to #8

Approval Criteria		
8. Is the request for prophylactic therapy and there is documentation that the patient has experienced 4 or more migraine days in the previous month AND the patient is an adult (18 years or older)?	**Yes:** Document migraine days per month _____ Go to # 9	**No:** Pass to RPh. Deny; medical appropriateness
9. Has the patient had an adequate trial (2-6 months) without response, or has contraindications, to at least 3 of the following OHP preferred drugs (in the same or different classes)? • Propranolol immediate-release, metoprolol, or atenolol • Topiramate, valproic acid, or divalproex sodium • Amitriptyline, nortriptyline, or venlafaxine OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to the above migraine prophylaxis agents?	**Yes:** Document agents used and dates _____ _____ Go to # 10	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred alternatives at www.orpdl.org/drugs/
10. Is the request for erenumab and the patient has pre-existing hypertension or risk factors for hypertension?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #11
11. Has the patient received an injection with botulinum toxin for headache treatment once in the previous 2 months?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 3 months
12. In a patient with acute migraines, has the patient failed to receive benefit from adequate trials of abortive therapy (2 or more different triptans) or have contraindications to triptans?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness. Recommend triptan trial.
13. Does the patient have chronic migraines?	**Yes**: Go to #14	**No**: Approve for 3 months

Approval Criteria		
14. Does the patient have a history of at least 4 migraines a month AND is on preventative migraine therapy (excluding other CGRP inhibitors)?	**Yes:** Approve for up to 3 months	**No:** Pass to RPh. Deny; medical appropriateness
15. Has the patient failed to receive benefit from at least 2 cluster headache preventative treatments (i.e., lithium, verapamil, melatonin, prednisone, suboccipital steroid injection, topiramate)?	**Yes**: Approve for up to 3 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to #2
2. Is the renewal request for acute migraine treatment?	**Yes:** Go to #5	**No:** Go to #3
3. Is the renewal request for migraine prevention?	**Yes:** Go to #4	**No:** Go to # 6
4. Has the patient experienced a documented positive response to therapy, as demonstrated by a reduction in migraine headache frequency and/or intensity from baseline?	**Yes:** Document response. Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness
5. Has the patient demonstrated a response to therapy as indicated by a reduction in headache frequency and/or intensity?	**Yes:** Document response Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness
6. Is the renewal request for cluster headache prevention?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical Appropriateness

7. Does the patient have documentation of a positive response, indicated by a reduction in the number of cluster headaches per month?	**Yes:** Document response Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness

P&T/DUR Review: 6/23 (DE); 10/21 (KS), 8/20 (KS); 5/19; 9/18 (DE)
Implementation: 7/1/23; 1/1/2022; 11/1/2018