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OHSU Drug Effectiveness Review Project Summary Report - Calcitonin Gene-Related Peptide Inhibitors

Date of Review: August 2020

Date of Last Review: May 2019
Literature Search: 08/01/18-06/17/20

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

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 quality of life?
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)?
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 2020 Drug Effectiveness Review Project (DERP) report on CGRP inhibitors.[1] Drugs included in the review are eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant and ubrogepant (**Table 1**). Evidence suggests modest efficacy for the prevention of migraine and treatment of acute migraine and small differences in quality of life scores, with improvements of less than 10%.[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 1.8 to 3.5 days a month) compared to placebo. [1]
- Quality of life was improved, compared to placebo, with the use of eptinezumab, erenumab, fremanezumab and galcanezumab based on moderate quality of evidence.

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

- The number of migraine days per month were reduced with eptinezumab, erenumab, fremanezumab and galcanezumab compared to placebo, difference ranging from -0.7 to -2.8 days (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.

*Acute Migraine Treatment **(Table 4**)*

- For the outcome of freedom from pain at 2 hours rimegepant and ubrogepant were more effective than placebo, by a difference of 6.4% to 16.6% more patients experiencing pain freedom, based on moderate quality of evidence.[1]

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Cluster Headache Prevention

- Galcanezumab was more effective for the prevention of cluster headache compared to placebo with 3.5 (95% CI, -0.2 to -6.7) fewer attacks per week, for weeks 1-3 (low quality of evidence).[1] There is low quality evidence from one randomized trial that there is no difference between galcanezumab and placebo in cluster headache prevention at week 8.
- There was only low quality of evidence available for the comparison of adverse events between CGRP inhibitors and placebo for all treatment studied. Adverse events, severe adverse events and discontinuations due to adverse events were similar to placebo for the majority of CGRP inhibitors.
- There is insufficient evidence for the use of CGRP inhibitors in different subgroups and evidence of use beyond 24 weeks.

Recommendations:

- After clinical review no changes to the PDL are warranted.
- Update prior authorization (PA) criteria to include acute migraine treatments, rimegepant and ubrogepant, and indication for cluster headache for galcanezumab.
- After executive session, recommend galcanezumab be made preferred but subject to clinical PA criteria.

Summary of Prior Reviews and Current Policy

- A review in May of 2019 maintained 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. There are no preferred therapy options.
- There were 33 claims for CGRP inhibitors of quarter 1 of 2020 for Oregon Health Plan (OHP) Fee-for-Service (FFS) population. Each claim represents a significant cost to the OHP.

Methods:

The April 2020 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.

The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publicly available in the agenda packet and on the DURM website.

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. There are 6 CGRP inhibitors approved for migraine treatment in adults **(Table 1).**

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

Drug	Manufacturer	Dose	Approval Date	Approved Indication	Number of identified Studies
Eptinezumab VYEPTI	Alder Biopharmaceuticals, Inc.	100 mg or 300 mg IV every 3 monthsł	February 2020	Migraine Prevention	3
Erenumab AIMOVIG	Amgen	70 mg or 140 mg SC every monthł	May 2018	Migraine Prevention	6
Fremanezumab AJOVY	Teva Pharmaceuticals	225 mg SC monthly or 675 mg SC every 3 months	September 2019	Migraine Prevention	5
Galcanezumab* EMGALITY	Eli Lilly	Migraine: 120 mg SC every month Cluster: 300 mg SC every month	September 2018 and June 2019	Migraine Prevention Cluster Headache Prevention	6
Rimegepant ZYDIS	Biohaven Pharmaceuticals	75 mg orally as needed for acute migraine attack	February 2020	Acute Migraine Treatment	3
Ubrogepant UBRELVY	Allergan	50 mg, 100 mg orally as needed for acute migraine attack	December 2019	Acute Migraine Treatment	4

Abbreviations: IV – intravenously; SC – subcutaneously

Key: * Initial loading dose of 240 mg followed by a monthly dose of 120 mg; ł Some patients may benefit from the 300 mg dose

The purpose of this DERP report is to update evidence for the use of CGRP inhibitors since the last published update in October 2018.[1] Literature was searched through March 31, 2020. Main outcomes of interest were migraine events (symptoms, function, disability and quality of life), use of rescue therapies, employment related outcomes, health care utilization and adverse events. Quality of life assessment tools used for the determination of headache severity were the 6-item Headache Impact Test (HIT-6), Migraine-specific Quality of Life Score (MSQL) and Migraine Disability Assessment (MIDAS). 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”. Higher HIT-6 scores are related to a greater impact on quality of life with a range of 36-78 points. A change of 2.3 units has been suggested as the minimal clinically important difference (MCID). 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. 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. The MIDAS test is used to quantify headache disability based on a 7-item questionnaire. The score is based off of activity limitations ranging from little or no disability to severe disability. Scores of 0-5 are indicative of little or no disability, 6-10 mild disability, 11-20 moderate disability, and 21 or greater as severe disability. For many of the quality of life assessments there are not well defined minimal clinically important differences related to the treatment effect. A total of 14 new randomized controlled trials were identified, to bring the total trial inclusion number to 27. All trials but one was placebo-controlled and there was insufficient evidence for the direct comparison of CGRP inhibitors. The quality of studies was considered fair, with the exception of 1 poor quality trial.

Chronic Migraine Prevention

Eptinezumab, erenumab, fremanezumab, and galcanezumab are used for the prevention of chronic migraine.[1] With the exception of fremanezumab, all other therapies were studied in one randomized controlled trial. Patients in the studies had a mean of 14.1 to 19.6 migraine days per month. Outcomes with moderate evidence are presented in **Table 2**.[1] All of the therapies were found to be more effective than placebo for the outcomes of number of migraine days per month, days with acute medication use per month, and for the percent of patients with a 50% reduction in migraine days. The evidence for serious adverse events and discontinuations due to adverse events were associated with low or very low quality of evidence.

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

Outcome	Results	Quality of Evidence	Evidence Conclusion
Eptinezumab (every 3 months) vs. Placebo			
Migraine days per month	*Dodick et al* Eptinezumab 300 mg vs. Placebo -2.7 days (95%CI, -4.4 to -0.9) P=0.003 Eptinezumab 100 mg vs. Placebo -2.1 days (95% CI, -3.8 to -0.4) P=0.018 Eptinezumab 30 mg vs. Placebo -2.4 days (95% CI, -4.0 to -0.7) P=0.005 Eptinezumab 10 mg vs. Placebo -1.2 days (95% CI, -2.9 to 0.6) P=0.180	Moderate	Eptinezumab 30 mg, 100 mg and 300 mg are more effective than placebo for reducing the number of migraine days per month by an approximate decrease of 2 days.
Percentage of patients with at least 50% reduction in number of migraine days per month	*Dodick et al* Eptinezumab 300 mg single dose: 38 (33.3%) Eptinezumab 100 mg single dose: 37 (31.4%) Eptinezumab 30 mg single dose: 33 (28.2%) Eptinezumab 10 mg single dose: 33 (26.8%) Placebo: 24 (20.7%) Eptinezumab 300 mg vs. Placebo P=0.033 Eptinezumab 100 mg vs. Placebo P=0.072	Moderate	Eptinezumab 300 mg was more effective than placebo for the odds of a patient experiencing at least a 50% decrease in number of migraine days per month (ARR 12.6%/NNT 8)

	Eptinezumab 30 mg vs. Placebo P=0.201 Eptinezumab 10 mg vs. Placebo P=0.294		
Mean change in HIT-6	*Dodick et al* Eptinezumab 300 mg vs. Placebo -4.2 points (95%CI, -6.3 to -2.1) P<0.001 Eptinezumab 100 mg vs. Placebo -1.1 points (95% CI, -3.1 to 0.88) P=0.27 Eptinezumab 30 mg vs. Placebo -0.7 points (95% CI, -2.7 to 1.3) P=0.49 Eptinezumab 10 mg vs. Placebo -0.7 points (95% CI, -2.7 to 1.3) P=0.50	Moderate	Eptinezumab 300 mg was more effective than placebo at improving HIT-6 scores by approximately 4 points (5% change)
Erenumab (monthly) vs. Placebo			
Mean change in migraine days per month	*Tepper et al* Erenumab 70 mg vs. Placebo: -2.5 (95% CI, -3.5 to -1.4) P<0.0001 Erenumab 140 mg vs. Placebo: -2.5 (95% CI, -3.5 to -1.4) P<0.0001	Moderate	Erenumab 70 mg and 140 mg were more effective than placebo in reducing the number of migraine days by 2.5 days per month
Days with acute migraine medication use per month	*Tepper et al* Erenumab 70 mg vs. Placebo: -1.9 (95% CI, -2.6 to -1.1) P<0.0001 Erenumab 140 mg vs. Placebo: -2.6 (95% CI, -3.3 to -1.8)	Moderate	Erenumab 70 mg and 140 mg were more effective than placebo in reducing the need for migraine medication days per month by approximately 2 days

	P<0.0001		
Percentage of patients with at least 50% reduction in number of migraine days per month	*Tepper et al* Erenumab 70 mg vs. Placebo: OR 2.2 (95% CI, 1.5 to 3.3) P=0.0001 Erenumab 140 mg vs. Placebo: OR 2.3 (95% CI, 1.6 to 3.5) P<0.0001	Moderate	Erenumab 70 mg and 140 mg were more effective at increasing the odds of a patient experiencing at least 50% reduction in number of migraine days
Mean change in HIT-6 of 5 points or greater	*Tepper et al* Erenumab 70 mg vs. Placebo: OR 2.3 (95% CI, 1.5 to 3.4) P< 0.001 Erenumab 140 mg vs. Placebo: OR 2.3 (95% CI, 1.5 to 3.4) P<0.001	Moderate	Erenumab 70 mg and 140 mg were more effective than placebo in improving HIT-6 scores by ≥ 5 points
Fremanezumab (monthly) vs. Placebo			
Migraine days per month	*Bigal et al** Fremanezumab 225 mg vs. Placebo -1.7 days (95% CI, -3.7 to 0.2) P=0.08 Fremanezumab 900 mg vs. Placebo -2.0 days (95% CI, -3.9 to -0.1) P=0.04 *Silberstein et al** Fremanezumab 225 mg vs. Placebo -2.1 days P<0.001 Fremanezumab 675 mg quarterly vs. Placebo -1.8 days P<0.001 *Ferrari et al†* Fremanezumab 675 mg quarterly vs. Placebo -3.1 days (95% CI, -3.8 to -2.4)	Moderate	Fremanezumab 225 mg, 675 mg, 900 mg were more effective than placebo in reducing migraine days by 2-3 days per month; however, one study of the 225 mg strength found no statistically significant difference between placebo and active treatment

	P<0.0001 Fremanezumab 225 mg monthly vs. Placebo -3.5 (95% CI, -4.2 to -2.8) P<0.001		
Days with acute migraine medication use per month	*Bigal et al** Fremanezumab 225 mg vs. Placebo -2.2 (95% CI, -4.0 to 0.3) P=0.02 Fremanezumab 900 mg vs. Placebo -2.0 (95% CI, -3.9 to -0.20) P=0.03 *Silberstein et al** Fremanezumab 225 mg vs. Placebo -2.3 days P<0.001 Fremanezumab 675 mg quarterly vs. Placebo -1.8 days P<0.001 *Ferrari et al†* Fremanezumab 675 mg quarterly vs. Placebo -3.1 days (95% CI, -3.8 to -2.4) P<0.0001 Fremanezumab 225 mg monthly vs. Placebo -3.4 (95% CI, -4.0 to -2.7) P<0.0001	Moderate	Fremanezumab 225 mg, 675 mg and 900 mg were more effective than placebo reducing the number of days with acute migraine medication use per month
Percentage of patients with at least 50% reduction in number of migraine days per month	*Silberstein et al** Fremanezumab 225 mg: 153 (41%) Placebo: 67 (18%) RR 2.3 (95% CI, 1.8 to 2.9) P<0.001 Fremanezumab 675 mg quarterly:	Moderate	Fremanezumab 225 mg and 675 mg were more effective than placebo at increasing the odds of a patient experiencing at least 50% reduction in the number of migraines days per month

	141 (38%) Placebo: 67 (18%) RR 2.1 (95% CI, 1.6 to 2.7) P<0.001 *Ferrari et al†* Fremanezumab 675 mg quarterly vs. Placebo OR 5.8 (95% CI, 3.6 to 9.6) P<0.0001 Fremanezumab 225 mg monthly vs. Placebo 5.8 (95% CI, 3.6 to 9.5) P<0.001		
Mean change in HIT-6	*Silberstein et al** Fremanezumab 225 mg vs. Placebo -2.4 points P<0.001 Fremanezumab 675 mg quarterly vs. Placebo -1.9 days P<0.001	Moderate	HIT-6 scores were improved with fremanezumab 225 mg and 675 mg more than those treated with placebo by 2 points (3% change)
Galcanezumab (monthly) vs. Placebo			
Migraine days per month	*Detke et al* Galcanezumab 120 mg vs. Placebo -2.1 days (95% CI, -2.9 to -1.3) P<0.001 Galcanezumab 240 mg vs. Placebo -1.9 days (95% CI, -2.7 to -1.1) P<0.001	Moderate	Galcanezumab 120 mg and 240 mg were more effective than placebo in reducing migraine days by approximately 2 days per month
Percentage of patients with at least 50% reduction in number of migraine days per month	*Detke et al* Galcanezumab 120 mg vs. Placebo OR 2.1 (95% CI, -1.6 to -2.8) P<0.001 Galcanezumab 240 mg vs. Placebo OR 2.1 (95% CI, 1.6 to 2.8) P<0.001	Moderate	The odds of a patient experiencing at least a 50% reduction in number of migraine days per month was higher in patients treated with galcanezumab 120 mg and 240 mg compared to placebo

Days with acute headache days per month	*Detke et al* Galcanezumab 120 mg vs. Placebo -2.5 days (95% CI, -3.3 to -1.8) P<0.001 Galcanezumab 240 mg vs. Placebo -2.0 days (95% CI, -2.8 to -1.3) P<0.001	Moderate	Galcanezumab 120 mg and 240 mg were more effective than placebo in reducing the number of acute headache days by approximately 2 days per month
Mean change in MSQL (functioning-preventive score)	*Detke et al* Galcanezumab 120 mg vs. Placebo 7.0 (95% CI, 4.2 to 9.8) P<0.001 Galcanezumab 240 mg vs. Placebo 5.1 (95% CI, 2.3 to 7.9) P<0.001		Galcanezumab 120 mg and 240 mg improved functioning more than placebo by approximately 6%

Abbreviations: ARR – absolute risk reduction; CI – confidence interval; HIT-6 – Six-item Headache Impact Test; MD – mean difference; MSQL – Migraine Specific Quality of Life Score; OR – odds ratio; RR – relative risk

Key: * Patients in the 225 mg group were given fremanezumab 675 mg at baseline and 225 mg of fremanezumab at weeks 4 and 8; † Patients in the fremanezumab 225 mg group received an initial dose of 675 mg

Episodic Migraine Prevention

Drugs studied for episodic migraine prevention include eptinezumab, erenumab, fremanezumab, and galcanezumab. Patients had a history of 6.6 to 11.3 migraine 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 approximately 2 days (**Table 3**). The evidence for serious adverse events and discontinuations due to adverse events were similar to placebo (low quality of evidence).

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

Outcome	Results	Quality of Evidence	Evidence Conclusions
Eptinezumab (every 3 months) vs. Placebo			
Migraine days per month	*Ahina et al* Eptinezumab 30 mg vs. Placebo -0.82 (95% CI, -1.39 to -0.25) P=0.0046 Eptinezumab 100 mg vs. Placebo -0.69 (95% CI, -1.25 to -0.12) P=0.02	Moderate	Eptinezumab 30 mg, 100 mg, 300 mg and 1000 mg were more effective than placebo in reducing migraine days by approximately 1 day per month

	Eptinezumab 300 mg vs. Placebo -1.11 (95% CI, -1.68 to -0.54) P=0.0001 *Dodick et al* Eptinezumab 1,000mg vs. Placebo -1.0 days (95% CI, -2.0 to 0.1) P=0.0306		
Percentage with at least 50% reduction in number of migraine days per month	*Ahina et al* Eptinezumab 30 mg vs. Placebo 12.8% (95% CI, 3.7% to 21.5%) ARR 12.8%/NNT 8 P=0.006 Eptinezumab 100 mg vs. Placebo 12.4% (95% CI, 3.2% to 21.5%) ARR 12.4%/NNT 8 P=0.009 Eptinezumab 300 mg vs. Placebo 18.9% (95% CI, 9.8% to 28.0%) ARR 18.9%/NNT 5 P=0.0001 *Dodick et al* Eptinezumab 1,000mg: 56 (73%) Placebo: 52 (67%) RR 1.15 (95% CI, 0.94 to 1.41) P=0.21	Moderate	Eptinezumab 30 mg, 100 mg and 300 mg were more effective than placebo at increasing the odds of patients experiencing at least 50% reduction in number of migraine days per month with a benefit of 12% to 19% patients (NNT 5-17)
Erenumab (monthly) vs. Placebo			
Migraine days per month	*Reuter et al* Erenumab 140 mg vs. Placebo -1.6 (95% CI, -2.7 to -0.5) P=0.004 *Sakai et al* Erenumab 70 mg vs. Placebo -2.3 (95% CI, -3.0 to -1.6)	Moderate	Erenumab 70 mg and 140 mg were more effective than placebo in reducing the number of migraine days per month by approximately 2 days

	P<0.001 Erenumab 140 mg vs. Placebo -1.9 (95% CI, -2.6 to -1.2) P<0.001 *Dodick et al* Erenumab 70 mg vs. Placebo -1.0 (95% CI, -1.6 to -0.5) P<0.001 *Goadsby et al* Erenumab 70 mg vs. Placebo -1.4 (95% CI, -1.9 to -0.9) P<0.001 Erenumab 140 mg vs. Placebo -1.9 (95% CI, -2.3 to -1.4) P < 0.001 *Sun et al* Erenumab 70 mg vs. Placebo -1.1 (95% CI, -2.1 to -0.2) P=0.02		
Days with acute migraine medication use per month	*Reuter et al* Erenumab 140 mg vs. Placebo -1.7 (95% CI, -2.4 to -1.0) P<0.001 *Sakai et al* Erenumab 70 mg vs. Placebo -2.1 (95% CI, -2.7 to -1.5) P<0.001 Erenumab 140 mg vs. Placebo -2.0 (95% CI, -2.6 to -1.5) P<0.001	Moderate	Erenumab 70 mg and 140 mg were more effective than placebo in reducing the days with acute migraine medication use per month by approximately 2 days

	Dodick et al Erenumab 70 mg vs. Placebo -0.6 (95% CI, -1.0 to -0.2) P=0.002 *Goadsby et al* Erenumab 70 mg vs. Placebo -0.9 (95% CI, -1.2 to -0.6) P < 0.001 Erenumab 140 mg vs. Placebo -1.4 (95% CI, -1.7 to -1.1) P < 0.001 *Sun et al* Erenumab 70 mg vs. Placebo -1.0 (95% CI, -1.6 to -0.3) P=0.004		
Percentage of patients with at least 50% reduction in number of migraine days per month	*Reuter et al* Erenumab 140 mg vs. Placebo OR 1.7 (95% CI, -2.4 to -1.0) P<0.001 *Sakai et al* Erenumab 70 mg vs. Placebo OR 5.6 (95% CI, 2.6 to 12.1) P<0.001 Erenumab 140 mg vs. Placebo OR 4.7 (95% CI, 2.2 to 10) P<0.001 *Dodick et al* Erenumab 70 mg: 112 (39.7%) Placebo: 85 (29.5%) OR 1.59 (95% CI, 1.12 to 2.27) P=0.01	Moderate	Erenumab 70 mg and 140 mg were more effective in percentage of patients with at least 50% reduction in the number of migraine days per month

	Goadsby et al Erenumab 70 mg: 135 (43.3%) Placebo: 84 (26.6%) OR 2.13 (95% CI, 1.52 to 2.98) P<0.001 Erenumab 140 mg: 159 (50.0%) Placebo: 84 (26.6%) OR 2.81 (95% CI, 2.01 to 3.94) P<0.001 *Sun et al* Erenumab 70 mg: 46 (46%) Placebo: 43 (30%) OR 2.0 (95% CI, 1.2 to 3.4) P=0.01		
Mean change in HIT-6	*Sakai et al* Erenumab 70 mg vs. Placebo -2.1 points (95% CI, -3.3 to -0.9) P<0.001 Erenumab 140 mg vs. Placebo -2.0 points (95% CI, -3.2 to -0.8) P=0.001 *Dodick et al* Erenumab 70 mg vs. Placebo -2.3 points (95% CI, -3.3 to -1.3) P<0.001 *Goadsby et al* Erenumab 70 mg vs. Placebo -2.1 points (95% CI, -3.0 to -1.1) P<0.001 Erenumab 140 mg vs. Placebo -2.3 points (95% CI, -3.2 to -1.3) P<0.001	Moderate	Erenumab 70 mg and 140 mg were more effective at improving HIT-6 scores compared to placebo by approximately 2 points (3% change)

	Sun et al Erenumab 70 mg vs. Placebo -1.0 points (95% CI, -2.5 to -0.6) P=0.22		
Fremanezumab (monthly) vs. Placebo			
Migraine days per month	*Bigal et al* Fremanezumab 225 mg vs. Placebo -2.8 days (95% CI, -4.1 to -1.6) P-value not reported Fremanezumab 675 mg vs. Placebo -2.6 days (95% CI, -3.9 to -1.3) P-value not reported *Dodick et al* Fremanezumab 225 mg monthly vs. Placebo -1.5 days (95% CI, -2.0 to -0.93) P<0.001 Fremanezumab 675 mg quarterly vs. Placebo -1.3 days (95% CI, -1.8 to -0.72) P<0.001	Moderate	Fremanezumab 225 mg and 675 mg were more effective than placebo in reducing the number of migraine days per month by approximately 2 days
Days with acute headache medication use per month	*Bigal et al* Fremanezumab 225 mg vs. Placebo -1.8 (95% CI, -2.9 to -0.66) P-value not reported Fremanezumab 675 mg vs. Placebo -1.7 (95% CI, -2.8 to -0.60) P-value not reported *Dodick et al* Fremanezumab 225 mg monthly vs. Placebo -1.4 days (95% CI, -1.8 to -0.89) P<0.001	Moderate	Fremanezumab 225 mg and 675 mg were more effective than placebo in reducing the days with acute headache medication use per month by 1- 2 days

	Fremanezumab 675 mg quarterly vs. Placebo -1.3 days (95% CI, -1.8 to -0.82) P<0.001		
Percentage of patients with at least 50% reduction in number of migraine days per month	*Bigal et al* Fremanezumab 225 mg: 53 (56%) Fremanezumab 675 mg: 55 (57%) Placebo: 36 (35%) Fremanezumab 225 mg vs. Placebo RR 1.61 (95% CI, -.17 to 2.22) P=0.003 Fremanezumab 675 mg vs. Placebo RR 1.66 (95% CI, 1.21 to 2.27) P=0.002 *Dodick et al* Fremanezumab 225 mg monthly: 137 (47.7%) Fremanezumab 675 mg quarterly: 128 (44.4%) Placebo: 81 (27.9%%) Fremanezumab 225 mg vs. Placebo RR 1.71 (95% CI, 1.37 to 2.13) P<0.001 Fremanezumab 675 mg vs. Placebo RR 1.59 (95% CI, 1.27 to 2.99) P<0.001	Moderate	Fremanezumab 225 mg and 675 mg were more effective than placebo in increasing the percent of patients with at least 50% reduction in number of migraine days per month
Mean change in MIDAS score	*Bigal et al* Fremanezumab 225 mg vs. Placebo -14.5 points (95% CI, -26.8 to -2.2) P-value not reported Fremanezumab 675 mg vs. Placebo -15.2 points (95% CI, -27.6 to -2.8)	Moderate	Fremanezumab 225 mg and 675 mg were more effective than placebo in improving quality of life, based on a change in MIDAS score of 5-15 points

	P-value not reported *Dodick et al* Fremanezumab 225 mg monthly vs. Placebo -7.0 points (95% CI, -10.5 to -3.5) P<0.001 Fremanezumab 675 mg quarterly vs. Placebo -5.4 points (95% CI, -8.9 to -1.9) P=0.002		
Galcanezumab (monthly) vs. Placebo			
Migraine days per month	*Dodick et al* Galcanezumab 150 mg every 2 weeks vs. Placebo MD -1.2 (95% CI, -1.9 to -0.6) P=0.003 *Ksljarevski et al* Galcanezumab 120 mg monthly MD -2.0 days (95% CI, -2.6 to -1.5) P=0.026 Galcanezumab 240 mg monthly MD -1.9 days (95% CI, -2.4 to -1.4) P=0.026 *Skljarevski et al* Galcanezumab 120 mg v. Placebo -0.9 (no CI provided) P=0.02 Galcanezumab 300 mg -0.9 (no CI provided) P=0.02 *Stauffer, et al* Galcanezumab 120 mg vs. Placebo	Moderate	Galcanezumab 120 mg, 150 mg, 240 mg and 300 mg reduced the number of migraine days per month by approximately 1-2 days compared to placebo

	-1.9 (95% CI, -2.5 to -1.4) P<0.001 Galcanezumab 240 mg vs. Placebo -1.8 (95% CI, -2.3 to -1.2) P<0.001		
Percentage of patients with at least 50% reduction in number of migraine days per month	*Dodick et al* Galcanezumab 150 mg: 69 (70.4%) Placebo: 47 (45.2%) OR 2.88 (95% CI, 1.61 to 5.18) *Skljarevski et al* Galcanezumab 120 mg: 137 (59.3%) Galcanezumab 240 mg: 126 (56.5%) Placebo: 233 (36.0%) Galcanezumab 120 mg vs. Placebo RR 1.65 (95% CI, 1.40 to 1.94) P=0.025 Galcanezumab 240 mg vs. Placebo RR 1.57 (95% CI, 1.33 to 1.86) P=0.025 *Skljarevski et al* Galcanezumab 120 mg: 47 (75.8%) Galcanezumab 300 mg: 78 (61.9%) RR 1.22 (95% CI, 1.01 to 1.49) P=0.07 *Stauffer et al* Galcanezumab 120 mg: 131 (62.3%) Galcanezumab 240 mg: 127 (60.9%) Placebo: 164 (95% CI, 38.6%) Galcanezumab 120 mg vs. Placebo OR 2.6 (2.0 to 3.4) P<0.001	Moderate	Galcanezumab 120 mg, 150 mg, 240 mg and 300 mg increased the percentage of patients with at least 50% reduction in number of migraine days per month

	Galcanezumab 240 mg vs. Placebo OR 2.5 (95% CI, 1.9 to 3.2) P<0.001		
Mean change in MIDAS score	*Ksljarevski et al* Galcanezumab 120 mg monthly -9.2 points (95% CI, -11.8 to -6.6) P<0.001 Galcanezumab 240 mg monthly -8.2 points (95% CI, -10.5 to -5.9) P<0.001 *Stauffer et al* Galcanezumab 120 mg vs. Placebo -6.3 points (no CI reported) P<0.001 Galcanezumab 240 mg vs. Placebo -5.2 points (no CI reported) P<0.002	Moderate	Mean change in MIDAS scores were more improved in patients taking 120 mg and 240 mg compared to placebo

Abbreviations: ARR – absolute risk reduction; CI – confidence interval; HIT-6 – Six-item Headache Impact Test; MD – mean difference; MIDAS – Migraine Disability Assessment; NNT – number needed to treat; OR – odds ratio; RR – relative risk

Acute Migraine Treatment

Rimegepant and ubrogepant are two new CGRP inhibitors used for the acute treatment of migraine. Both therapies were studied in 3 randomized controlled trials (Table 4).[1] 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.

Table 4. CGRP Inhibitors for Acute Migraine Treatment[1]

Outcome	Results	Quality of Evidence	Evidence Conclusions
Rimegepant vs. Placebo			
Freedom from pain at 2 hours post-dose	*Marcus et al* Rimegepant 75 mg: 27 (31.4%) Placebo: 32 (15.3%) RR 2.1 (95% CI, 1.3 to 3.2) P<0.05	Moderate	Rimegepant 75 mg was more effective than placebo in increasing the number of patients who were free from pain at 2 hours (by approximately 15%) and was similar in efficacy to sumatriptan 75 mg

	Rimegepant 75 mg: 27 (31.4%) Sumatriptan: 35 (35.0%) RR 0.90 (95% CI, 0.6 to 1.4) P-value not reported *Croop et al* Rimegepant 75 mg vs. Placebo RD 10.4 (95% CI, 6.5 to 14.2) P<0.0001 *Lipton et al* Rimegepant 75 mg: 105 (19.6%) Placebo: 64 (12.0%) RR 1.6 (95% CI, 1.2 to 2.2) P<0.001		
Freedom from most bothersome symptom at 2 hours post-dose	*Croop et al* Rimegepant 75 mg vs. Placebo RD 8.3 (95% CI, 3.4 to 13.2) P=0.0009 *Lipton et al* Rimegepant 75 mg: 202 (37.6%) Placebo: 135 (25.2%) RR 1.5 (95% CI, 1.3 to 1.8) P<0.001	Moderate	Rimegepant 75 mg was more effective than placebo in the number of patients with freedom from the most bothersome symptom at 2 hours
Ubrogepant vs. Placebo			
Freedom from pain at 2 hours post-dose	*Voss et al* Ubrogepant 50 mg: 22 (21.0%) Placebo: 10 (8.9%) RR 2.4 (95% CI, 1.2 to 4.7) *Dodick et al* Ubrogepant 50 mg: 81 (19.2%) Placebo: 54 (11.8%) OR 1.83 (95% CI, 1.25 to 2.66) P=0.01	Moderate	Freedom from pain at 2 hours was higher, by an average of 9%, in the number of patients taking ubrogepant 50 mg and 100 mg compared to placebo

	Ubrogepant 100 mg: 95 (21.2%) Placebo: 54 (11.8%) OR 2.04 (95% CI, 1.41 to 2.95) P<0.001 *Lipton et al* Ubrogepant 50 mg: 101 (21.8%) Placebo: 65 (14.3%) OR 1.62 (95% CI, 1.14 to 2.29) P=0.01		
Freedom from most bothersome symptom at 2 hours post-dose	*Dodick et al* Ubrogepant 50 mg: 162 (38.6%) Placebo: 126 (27.8%) OR 1.70 (95% CI, 1.27 to 2.28) P=0.002 Ubrogepant 100 mg: 169 (39.7%) Placebo: 126 (27.8%) OR 1.63 (95% CI, 1.22 to 2.17) P=0.02 *Lipton et al* Ubrogepant 50 mg: 180 (38.9%) Placebo: 125 (27.4%) OR 1.65 (95% CI, 1.25 to 2.20) P=0.01	Moderate	Freedom from the most bothersome symptom at 2 hours was higher in patients taking ubrogepant 50 mg and 100 mg compared to placebo
Ability to function normally within 2 hours post-dose	*Dodick et al* Ubrogepant 50 mg: 171 (40.6%) Placebo: 136 (29.8%) OR 1.67 (95% CI, 1.22 to 2.27) P-value not reported Ubrogepant 100 mg: 192 (42.9%) Placebo: 136 (29.8%) OR 1.93 (95% CI, 1.42 to 2.61) P-value not reported	Moderate	Ubrogepant 50 mg and 100 mg were more effective than placebo at improving ability to function normally within 2 hours

Abbreviations: CI – confidence interval; OR – odds ratio; RD – risk difference; RR – risk ratio

CGRP Inhibitors for Cluster Headache Prevention

Galcanezumab was studied for the use of cluster headache prevention in one randomized controlled trial.[1] There was low quality evidence of no difference between groups at 8 weeks.

Evidence Limitations

Evidence was downgraded due manufacturer sponsorship and involvement in the trials themselves. Some studies were also biased due to imprecision because of infrequent event occurrence. Trials were of short duration preventing long-term evidence for efficacy and harms in a condition that is treated on a chronic basis.

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; 2020.

Appendix 1: Current Preferred Drug List

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

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) antagonists (eptinezumab, erenumab, fremanezumab, galcanezumab, rimegepant and ubrogepant) pharmacy and physician 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
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
Ubrogepant	Acute migraine treatment

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Is this an FDA-approved indication (Table 1)?	**Yes**: Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the diagnosis funded by OHP?	**Yes:** Go to #4	**No:** 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?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #5
5. Is the medication being prescribed by or in consultation with a neurologist or headache specialist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness
6. Do chart notes indicate headaches are due to medication overuse?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Go to # 7
7. Is the request for acute migraine treatment AND the patient is an adult (18 years or older)?	**Yes:** Go to #12	**No:** Go to #8
8. 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 #9
9. Is there 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 # 10	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
10. Has the patient failed an adequate trial (≥6 weeks with a documented adherence of ≥80%) of an FDA-approved migraine prophylaxis medication from each of the following classes: beta-blockers, anticonvulsants, and tricyclic antidepressants? OR Does the patient have a documented intolerance, FDA-labeled contraindication, or hypersensitivity to each of the above migraine prophylaxis classes?	**Yes:** Document agents used and dates _____ _____ Go to # 11	**No:** Pass to RPh. Deny; medical appropriateness
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. Has the patient failed adequate trials (3 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
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. Does the patient have at least 4 headache attacks per week AND have a history of cluster headaches beyond one month?	**Yes:** Go to #16	**No:** Pass to RPh. Deny; medical appropriateness
16. Has the patient failed at least 2 cluster headache preventative treatments (i.e., lithium, verapamil, melatonin, frovatriptan, prednisone, suboccipital steroid injection, topiramate, and valproate)?	**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 (e.g. minimum 2 doses for treatment given every 3 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 reduction of at least 8 cluster headaches per month?	**Yes:** Document response Approve for up to 6 months	**No:** Pass to RPh. Deny; medical Appropriateness

P&T/DUR Review: 8/20 (KS); 5/19; 9/18 (DE)
Implementation: 11/1/2018