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Drug Class Update: CGRP Inhibitors

Date of Review: October 2021

Date of Last Review: August 2020
Dates of Literature Search: 06/01/2020 - 07/07/2021

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

Purpose for Class Update: The purpose for the calcitonin gene-related peptide (CGRP) inhibitors class update is to evaluate new literature published since the last update (August 2020) and to review the evidence for the new indication for rimegepant, with policy changes if needed.

Research Questions:
1. What is the new comparative evidence for efficacy and effectiveness for the 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:
- Evidence for CGRP inhibitors is limited to indirect treatment comparisons which prevents comparative efficacy assessment. There is insufficient evidence for outcomes assessing functional improvements and maintaining ability to work.
- An Agency for Healthcare Research and Quality (AHRQ) review found the use of CGRP inhibitors (rimegepant and urbrogepant) for the acute treatment of episodic migraine to be more effective than placebo for the outcomes of pain freedom at 2 hours and at 1 day based on moderate to high quality evidence. There were no significant differences in adverse event rates between CGRP inhibitors and placebo.[1]
- High quality guidance by the National Institute for Health and Care Excellence (NICE) for acute and chronic migraine support current policy.[2]
- In May of 2021 rimegepant received an expanded indication for use as a preventative therapy in adults with episodic migraine.[3] Approval was based off of one phase 2/3 study which demonstrated rimegepant 75 mg every other day reduced the mean migraine days per month by -0.8 more than placebo (95% Confidence Interval [CI], -1.46 to -0.20; p=0.0099).[4] Benefits are unlikely to be clinically significant.
- In May of 2021 erenumab updated labeling to include the warning of new-onset or worsening of pre-existing hypertension.[5]
- There were 4 new randomized controlled trials (RCT) published that support new and current indications for CGRP inhibitors.
- There was insufficient evidence on efficacy or harms data for subgroup populations.

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Recommendations:

- No changes to the preferred drug list (PDL) are warranted based on the evidence identified since the last review.
- After costs were evaluated in executive session, erenumab (Aimovig) was made preferred and galcanezumab (Emgality) was made non-preferred on the PDL.

Summary of Prior Reviews and Current Policy:

- CGRP inhibitors were last reviewed in August of 2020. Evidence was based off of a Drug Effectiveness Review Project (DERP) report on the use of CGRP inhibitors for migraine (e.g., acute, chronic, and episodic) and cluster headache. There was moderate quality of evidence for use of CGRP inhibitors for acute, episodic and chronic migraine. There was low quality evidence for the use of galcanezumab for use in cluster headache prevention.
- Fremanezumab and galcanezumab are preferred products on the PDL, but are subject to a clinical prior authorization (PA). Refer to **Appendix 1** for other drugs included in the CGRP class.

Background:

Migraine or severe headaches have been reported in 40 million adults in the United States (US), with a higher incidence occurring in women than men.[6] Migraine is a common headache ailment characterized by severe headache, nausea and/or vomiting, tingling, numbness, dizziness and increased sensitivity to sensory stimulation.[7] Migraine headaches may be associated with an aura, which are neurological sensations which may affect speech, vision, strength and sensations. Migraine severity can range from mild to severe and is known to impact quality of life, including missed work days, interference in personal relationships, social isolation, and lack the ability to do activities of daily living.[8] Factors that may predispose individuals to migraine include: emotional stress, menstruation, visual stimuli, weather changes, and certain foods or activities.[6]

Diagnosis of migraine is based on patient reported symptoms, and there is a lack of objective testing options to definitively diagnose migraine. Criteria has been developed by the International Classification of Headache Disorder to help classify migraine (**Table 1**).[7] Migraine is commonly characterized as either episodic or chronic based on headache frequency.[9] Episodic migraine is defined as patients with 15 migraines or less a month. Chronic migraine sufferers have more than 15 headache a month, with at least 8 of the headaches considered migraines.[9] Migraine may be associated with an aura, referring to the onset of sensory or motor symptoms occurring before or after headache onset.[10] Early treatment of migraine, in particular those with aura, is correlated with improved treatment outcomes.

Table 1. International Classification of Headache Disorders, 3rd edition (ICHD-3)[7]

Episodic Migraine	Chronic Migraine
A. At least 5 attacks fulfilling criteria B-D B. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated) C. Headache has at least 2 of the following characteristics: • Unilateral location • Pulsating quality • Moderate to severe pain intensity • Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) D. During headache at least one of the following:	A. Migraine-like or tension-type headache on ≥15 days/month for >3 months that fulfill criteria B and C B. Occurring in a patient who has had a least 5 attacks fulfilling criteria B-D for migraine without aura (which is the same criteria as B-D for episodic migraine) and/or criteria B and C for migraine with aura* C. On ≥8 days/month for >3 months, fulling any of the following: • Criteria C and D migraine without aura • Criteria B and C for migraine with aura • Believed by the patient to be migraine at onset and relieved by triptan or ergot derivative

• Nausea, vomiting, or both • Photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis	D. Not better accounted for by another ICHD-3 diagnosis
* One or more fully reversible aura symptoms (visual, sensory, speech and/or language, motor , brainstem [pain at back of head on both sides], retinal [affecting only one eye and may result in temporary blindness]) and at least three of the following six characteristics: 1. at least one aura symptom spreads gradually over ≥5 minutes 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5-60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive (e.g., flash hallucination, visual distortion) 6. the aura is accompanied, or followed within 60 minutes, by headache	

Treatment of migraine is divided into two types: acute (abortive) and preventative. Acute therapy is most effective when given as soon as symptoms appear. Common acute treatment options are nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, triptans (5-hydroxytryptamine [HT] 1b/1d agonists), antiemetics and ergot derivatives.[6] Acetaminophen and NSAIDs are recommended for mild to moderate migraine attacks that are not associated with severe nausea or vomiting. Patients that experience severe nausea or vomiting may be candidates for an oral or rectal antiemetic. Oral triptans or triptan/naproxen combination products are recommended first-line by AHRQ treatment guidelines for patients with moderate to severe migraine attacks[1] and are the most commonly used migraine specific treatment.[10] These recommendations are supported by NICE, which recommends triptans in combination with aspirin or acetaminophen, as the most cost-effective initial treatment.[11] Current triptan formulations result in approximately 50% of patients experiencing pain-freedom at 2 hours.[6] Triptan products also have the advantage of availability in oral, intranasal and subcutaneous formulations. Loss of triptan efficacy over time has been reported, and triptans are contraindicated in patients with cardiovascular disease.[10] Adverse events were found to be similar between different triptans by the Canadian Agency for Drugs and Technology in Health (CADTH).[12] For patients who do not tolerate triptans, ergotamine preparations are an option; however, adverse events and limited efficacy have resulted in low utilization.[10] Patients who experience a moderate to severe attack associated with vomiting or severe nausea may benefit from subcutaneous (SC) sumatriptan, nasal sumatriptan or zolmitriptan, non-oral antiemetics or parenteral dihydroergotamine.[6] Treatment recommendations for children and adolescents with migraine include ibuprofen and triptans.[13]

Patients with frequent attacks should be considered for preventative treatment to minimize the chance of overuse headaches which can occur when acute migraine medications are used more than 10 days per month or more than 15 days per month for aspirin, acetaminophen and NSAIDs. Preventative treatment is usually initiated when migraine occurs at least once per week or on 4 or more days per month. Preventative therapies with the most evidence for use include divalproex, metoprolol succinate, metoprolol tartrate, valproate acid, timolol, topiramate and propranolol. Atenolol, amitriptyline, nadolol, and venlafaxine have less robust evidence as preventative therapy but are also used.

Cluster headache is a debilitating headache condition which is four times more likely to effect men compared to women.[14] The frequency of attacks for individuals with cluster headache ranges from 1 every other day to 8 daily. Treatment for patients with cluster headache include acute treatment and prevention. Acute therapy consists of oxygen (100% with a flow rate of at least 12 litres/minute) or a triptan.[2,14] Second-line therapies include intranasal lidocaine, ergotamine and intravenous dihydroergotamine. Preventative therapy is a key component of cluster headache treatment, since acute therapy is useful for aborting the individual attack but has no effect on recurrent attacks.[15] Preventative therapy should be initiated immediately once the cluster headache attacks begin. Guidelines recommend verapamil first line for chronic cluster and episodic cluster that have relatively long-lasting active periods (i.e., 2 months or longer).[15] Glucocorticoids are recommended for patients with episodic cluster with active cluster periods that are less often, lasting less than 2 months. Glucocorticoids and dihydroergotamine can be used as adjunctive therapy to verapamil since it may take up to 2 weeks to titrate up to the effective verapamil dose. Galcanezumab is also considered an effective second-line preventative therapy. Nightly oral ergotamine can be used for attacks that only occur at night. Combination therapy, with prednisone, topiramate or lithium, can be considered for patients who lack symptom improvement on monotherapy.[15]

The most commonly studied intermediate outcomes related to the acute treatment of migraine headache include: headache pain improvement, headache pain freedom (ranging from 30 minutes to 2 hours), relief of most bothersome symptom (e.g., photophobia, phonophobia, nausea, or vomiting) and need for rescue medication. Disability, health-related quality of life, employment-related outcomes, and Patient Global Impression of Change (PGIC) are important health outcomes related to migraine. The PGIC is a scale ranging from 1-7 (very much worse to very much better) that is used to assess the patients' rating of overall improvement. The Migraine Disability Assessment Test (MIDAS) 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.[10] 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.[10]

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.

Table 1. FDA-Approved CGRP Inhibitors

Drug	Dose	Approval Date	Approved Indication
Eptinezumab VYEPTI[16]	100 mg or 300 mg IV every 3 months[ŧ]	February 2020	Migraine Prevention
Erenumab AIMOVIG[5]	70 mg or 140 mg SC every month[ŧ]	May 2018	Migraine Prevention
Fremanezumab AJOVY[17]	225 mg SC monthly or 675 mg SC every 3 months	September 2019	Migraine Prevention
Galcanezumab* EMGALITY[18]	Migraine: 120 mg SC every month Cluster: 300 mg SC every month	September 2018 and June 2019	Migraine Prevention Cluster Headache Treatment
Rimegepant NURTEC ODT[3]	75 mg orally as needed for acute migraine attack	February 2020 and May 2021	Acute Migraine Treatment Preventative Treatment of Episodic Migraine
Ubrogepant UBRELVY[19]	50 mg or 100 mg orally as needed for acute migraine attack	December 2019	Acute Migraine Treatment

Abbreviations: FDA – Food and Drug Administration, IV – intravenously; SC – subcutaneously
Key: * Initial loading dose of 240 mg followed by a monthly dose of 120 mg; [ŧ] Some patients may benefit from the 300 mg dose

There were 34 claims for CGRP inhibitors in the last quarter, which represents a moderate expenditure to the Oregon Health Authority (OHA). Forty-five percent were for preferred therapies.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits

used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

AHRQ – Acute Treatment for Episodic Migraine

A 2020 systematic review and meta-analysis by AHRQ was published on the acute treatment options for patients with episodic migraine.[1] Randomized controlled trials (135 trials) and comparative observational trials (6 trials) conducted in adults (18 years and older) searched up to July 2020 were included. Multiple drug classes were part of the review, including: triptans, dihydroergotamines (ergot derivative), antiemetics, acetaminophen, NSAIDs, opioids, CGRP antagonists and lasmiditan.[1] The CGRP inhibitors that were included were ubrogepant, rimegepant, telcagepant (not available in the United States) and BI 443070 (investigational therapy). Pain, function, pain relief satisfaction and quality of life were the primary outcomes of interest.

Findings were consistent with guideline recommendations that there is high-quality evidence for the use of triptans. Triptans were more effective than placebo for the ability to resolve pain at 2 hours and 1 day, with an associated increased risk of mild and transient adverse events.[1] There was moderate-quality evidence that NSAIDs, compared to placebo, resolve pain at 2 hours and 1 day, with an increased risk of mild and transient adverse events. Placebo-controlled comparisons also found dihydroergotamines, and ergotamines plus caffeine to resolve pain at 2 hours.[1] For newer therapies, lasmiditan was found to resolve pain at 2 hours based on high-quality evidence; however, serious adverse events were more common in patients treated with lasmiditan. Effectiveness for the use of opioids was associated with low-quality evidence.

A total of 14 trials were identified for CGRP inhibitors (n = 14,874), with an overall risk of bias of low to moderate for the included studies.[1] Rimegepant was studied in 3 clinical trials with doses ranging from 10 mg to 600 mg. There was moderate-quality evidence that more patients taking rimegepant were pain free at 2 hours compared to those taking placebo (relative risk [RR] 1.80; 95% CI, 1.52 to 2.13).[1] Pain freedom at 1 day was higher for rimegepant compared to placebo with a RR of 1.52 (95% CI, 1.33 to 1.74) (moderate-quality evidence).[1] The rimegepant trials were reported as having high risk of bias by the authors. Ubrogepant was associated with more patients experiencing pain freedom at 2 hours compared to placebo (RR 1.58; 95% CI, 1.31 to 1.90) and sustained pain freedom at 1 day (RR 1.63; 95% CI, 1.29 to 2.07) (high strength of evidence for both outcomes).[1] There were no significant differences in adverse events found between either urbrogepant or rimegepant when compared to placebo.

There is limited long-term data on adverse events of CGRP inhibitors. Many of the included studies only evaluated treatment one or few attacks, which may limit the capturing of harms data.

After review, 12 systematic reviews were excluded due to poor quality (e.g., indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[20–30]

New Guidelines:

NICE – Headaches in Over 12s: Diagnosis and Management

Guidance for the management of headaches was updated by NICE in May of 2021 which updated the clinical guidance originally published in 2012.[2] The focus of the guideline was to provide guidance on the diagnosis and management of tension-type headaches, migraine, cluster headache and medication overuse headache. Recommendations pertain to adults and young people, 12 years and older.[2] The focus of this review will be treatment updates related to migraine, with and without aura.[2]

Recommendations for acute migraine treatment:

- Combination therapy with an oral triptan and an NSAID or oral triptan and acetaminophen
- Patients preferring monotherapy should consider an oral triptan, NSAID, aspirin (900 mg), or acetaminophen
- For patients 12 to 17 years a nasal triptan should be considered over an oral triptan
- Patient preferences, comorbidities and risk of adverse events should be assessed before therapy initiation
- Patients that are unable to find symptom relief or do not tolerate recommended acute treatments (above) may consider a non-oral preparation of metoclopramide or prochlorperazine and a non-oral NSAID or triptan can be considered if they have not been tried.

NICE recommends the use of the most cost-effective triptan, with no recommendation for preference of one therapy over another.[2] The use of an anti-emetic, in addition to other acute treatments, is recommended even in the absence of nausea and vomiting. The use of ergots or opioids are not recommended for acute migraines. Gabapentin is not recommended for prophylactic treatment of migraine.[2] Prophylactic treatment of migraine should be re-evaluated 6 months after initiation. Hormonal contraceptives should not be routinely offered as contraception to women and girls who have migraine with aura. Women that are pregnant should manage migraines with acetaminophen. Triptans or NSAIDs can be considered if there is a need for additional treatment and the risks of medications use are discussed. A specialist should be consulted if prophylactic migraine therapy is needed during pregnancy.

Recommendations for prophylactic migraine treatment:

- Topiramate or propranolol is recommended after the risk and benefits are discussed.
- Patients should be made aware of fetal malformations and reduced effectiveness of hormonal contraceptives with topiramate.
- The use of effective contraception for women and girls of childbearing potential taking topiramate should be emphasized.
- If topiramate and propranolol are ineffective, then acupuncture can be offered for up to 10 sessions.
- Amitriptyline is also recommended if deemed appropriate after consideration of adverse events, comorbidities and patient's preferences.

Recommendations for menstrual-related migraine:

- Offer standard acute treatment. If symptom relief is not obtained consider frovatriptan (2.5 mg twice daily) or zolmitriptan (2.5 mg twice or three times daily) on days of an expected migraine.[2]

Recommendations for cluster headache:

- Acute treatment recommendations include oxygen and/or subcutaneous or nasal triptans
- Verapamil is recommended for prophylactic therapy. A specialist should be consulted if the patients does not respond to verapamil or if the patient is pregnant.

A safety update was added in 2021 for the use of topiramate for migraine prevention, to include patient discussions on the benefits and risks. Use of contraception for women and girls of childbearing potential should be emphasized when taking topiramate.[2]

Additional Guidelines for Clinical Context: none identified

After review, 1 guideline was excluded due to poor quality.[31]

New Indications:
Nurtec ODT (rimegepant) – In May of 2021 rimegepant received approval for preventative treatment of episodic migraine in adults.[3] Approval was based off of one, 12-week study of rimegepant use in adults (**Table 2**, Croop, et al).[3,4]

New FDA Safety Alerts:
Table 1. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Erenumab[5]	Aimovig	05/2021	Warnings and Precautions	Labeling was updated to include the warning of new-onset or worsening of pre-existing hypertension with the use of erenumab.

Randomized Controlled Trials:
A total of 38 citations were manually reviewed from the initial literature search. After further review, 34 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 4 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Croop, et al[4] DB, MC, PC, RCT, Phase 2/3	Rimegepant 75 mg orally every other day vs. Placebo orally every other day	Adults with at least 1 year history of migraine (with or without aura) or chronic migraine (n=747)	Change in mean number of migraine days per month from observation period to the last 4 weeks (weeks 9-12) in the double blind treatment period	Rimegepant: -4.3 Placebo: -3.5 LSMD -0.8 (95% CI, -1.46 to -0.20) P=0.0099 *Rimegepant was more effective than placebo for the reduction in the number of monthly migraines.*

	4 week OL observation period followed by double blinded 12 week treatment period			*The findings are not clinically significant with a decrease of less than 1 migraine per month compared to placebo.*
Lipton, et al[32] DB, MC, PC, RCT, Phase 3 (PROMISE-2)	Eptinezumab 100 mg IV vs. Eptinezumab 300 mg IV vs. Placebo IV Administered on day 0 and week 12	Adults with chronic migraine (baseline mean monthly migraine days was approximately 16.1) (n=1072)	Change from baseline in mean monthly migraine days (MMD) over weeks 1 to 12	Eptinezumab 100 mg: -7.7 Eptinezumab 300 mg: -8.2 Placebo: -5.6 Eptinezumab 100 mg vs. Placebo: MD -2.0 (95% CI, -2.9 to -1.2) P<0.0001 Eptinezumab 300 mg vs. Placebo: MD -2.6 (95% CI, -3.4 to -1.7) P<0.0001 *Both doses of eptinezumab were associated with an approximate reduction of 2 migraine days per month more than placebo.*
Mulleners, et al[33] (CONQUER) DB, MC, PC, RCT, Phase 3b	Galcanezumab 120 mg sc per month* [baseline migraines: 13.4] vs. Placebo sc [baseline migraines: 13.0] * Galcanezumab 240 mg sc loading dose Study duration: 3 months	Adults with episodic or chronic migraine, with migraine onset before the age of 50 who have failed 2-4 drug categories of preventative therapy in the past 10 years (n=462)	Mean change from baseline in number of monthly migraine headache days	Galcanezumab 120mg: -4.1 migraines Placebo: -1.0 migraines MD -3.1 (95% CI, -3.9 to -2.3) P<0.0001 *Galcanezumab was more effective than placebo for prevention of chronic or episodic migraine.* *Active treatment comparison would help determine the place in therapy for galcanezumab.*
Winner, et al[34]	Eptinezumab 100 mg IV	Adult patients with a greater	Co-primary efficacy end points were time to headache pain	Time to headache pain freedom: Eptinezumab: 4.0 hours

DB, MC, PC, RCT, Phase 3	vs. Placebo IV Both doses were given IV within 1-6 hours of onset of qualifying moderate to severe migraine	than 1-year history of migraine and migraine on 4 to 15 days per month in the 3 months prior to screening were treated during a moderate to severe migraine attack (based on *ICHD-3* criteria) (n=480)	freedom and time to absence of most of most bothersome symptom (nausea, photophobia, or phonophobia)	Placebo: 9.0 hours HR 1.54 (95% CI, 1.20 to 1.98) P<0.001 Absence of the most bothersome symptom: Eptinezumab: 2.0 hours Placebo: 3.0 hours HR 1.75 (95% CI, 1.41 to 2.19) P<0.001) *Eptinezumab shortened the time to headache and symptom resolution quicker than placebo in patients with an acute attack of a moderate to severe migraine. Eptinezumab is currently approved for migraine prevention only.*

Abbreviations: DB – double-blind; HR – hazard ratio; *ICHD-3* – *International Classification of Headache Disorders*, 3rd edition; IV – intravenous; LSMD – least squares mean difference; MC – multicenter; MD – mean difference; OL – open-label; PC – placebo-controlled; RCT - randomized clinical trial, SC - subcutaneous

References:

1. Halker Singh RB, VanderPluym JH, Morrow AS, et al. Acute Treatments for Episodic Migraine. Agency for Healthcare Research and Quality (AHRQ); 2020. doi:10.23970/AHRQEPCCER239.

2. National Institute for Health and Care Excellence. Headaches in over 12s: Diagnosis and Management. Clinical Guideline: CG150. Update May 2021.

3. Nurtec ODT (rimegepant) [prescribing information]. New Haven, CT; Biohaven Pharmaceuticals, Inc. May 2021.

4. Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. *Lancet*. 2021;397(10268):51-60. doi:10.1016/S0140-6736(20)32544-7.

5. Aimovig (erenumab-aooe) [prescribing information]. Thousand Oaks, CA; Amgen Inc. April 2020.

6. Smith J. Acute Treatment of Migraine in Adults. UpToDate. February 13, 2020.

7. International Headache Society. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalagia. 2018;38(1):1-211.

8. Canadian Agency for Drugs and Technologies in Health. Fremanezumab CADTH Reimbursement Recommendation. March 2021. Available at https://www.cadth.ca/fremanezumab. Accessed July 18, 2021.

9. The American Headache Society Position Statement On Integrating New Migraine Treatments Into Clinical Practice. *Headache: The Journal of Head and Face Pain*. 2019;59(1):1-18. doi:10.1111/head.13456.

10. Institute for Clinical and Economic Review. Acute Migraine: Final Evidence Report and Meeting Summary. ICER. Accessed February 27, 2020. https://icer-review.org/material/acute-migraine-final-evidence-report-and-meeting-summary/.

11. National Institute for Health and Clinical Excellence. Botulinum toxin type A for the prevention of headaches in adults with chronic migraine. NICE technology appraisal guidance 260. Published online June 2012. Accessed March 25, 2014. http://www.nice.org.uk/nicemedia/live/13776/59836/59836.pdf

12. Canadian Agency for Drugs and Technologies in Health. Triptans for Migraine Headaches: A Review of Clinical Evidence on Safety. March 23, 2012. Available at: https://www.cadth.ca/sites/default/files/pdf/htis/mar-2012/RC0333%20Triptans%20Final.pdf. Accessed March 3, 2020.

13. Richer L, Billinghurst L, Linsdell MA, et al. Drugs for the acute treatment of migraine in children and adolescents. *Cochrane Database Syst Rev*. 2016;4:CD005220. doi:10.1002/14651858.CD005220.pub2.

14. Francis G, Becker W,, Pringsheim T, et al. Acute and Preventative Pharmacologic Treatment of Cluster Headache. Neurology. 2010;75(5):463-73.

15. May, Arne. Cluster Headache Treatment and Prognosis. UpToDate. July 30, 2021.

16. Vyepti (eptinezumab) [prescribing information]. Bothell, WA; Lundbeck Seattle BioPharmaceuticals, Inc. February 2020.

17. Ajovy (fremanezumab) [prescribing information]. North Wales, PA. Teva Pharmaceuticals USA, Inc. January 2020.

18. Emgality (galcanezumab) [prescribing information]. Indianapolis, IN; Eli Lilly and Company. December 2019.

19. Ubrelvy (ubrogepant) [prescribing information]. Madison, NJ; Allergan USA, Inc. December 2019.

20. Zhao X, Xu X, Li Q. Efficacy and safety of galcanezumab for preventive treatment of migraine: a systematic review and meta-analysis. [Review]. *Journal of Neurology*. 2021;268(7):2364-2376. doi:10.1007/s00415-020-09707-5.

21. Smith TR, Spierings ELH, Cady R, et al. Safety and tolerability of eptinezumab in patients with migraine: a pooled analysis of 5 clinical trials. *The Journal of Headache and Pain*. 2021;22(1):16. doi:10.1186/s10194-021-01227-5.

22. Pellesi L, De Icco R, Alawie HY, et al. A systematic review, meta-analysis and meta-regression evaluating the adverse reactions to erenumab in the preventive treatment of migraine. *Expert Opinion on Drug Safety*. 2021;20(4):467-474. doi:10.1080/14740338.2021.1866537.

23. Zhang Z, Shu Y, Diao Y, et al. Calcitonin gene-related peptide receptor antagonist ubrogepant for the treatment of acute migraine: A meta-analysis. *Medicine*. 2021;100(8):e24741. doi:10.1097/MD.0000000000024741.

24. Ha DK, Kim MJ, Han N, Kwak J-H, Baek I-H. Comparative Efficacy of Oral Calcitonin-Gene-Related Peptide Antagonists for the Treatment of Acute Migraine: Updated Meta-analysis. *Clinical Drug Investigation*. 2021;41(2):119-132. doi:10.1007/s40261-020-00997-1.

25. Ford JH, Stauffer VL, McAllister P, et al. Functional impairment and disability among patients with migraine: evaluation of galcanezumab in a long-term, open-label study. *Quality of Life Research*. 2021;30(2):455-464. doi:10.1007/s11136-020-02632-0.

26. Yan Z, Xue T, Chen S, et al. Different dosage regimens of Eptinezumab for the treatment of migraine: a meta-analysis from randomized controlled trials. *Journal of Headache*. 2021;22(1):10. doi:10.1186/s10194-021-01220-y.

27. Ament M, Day K, Stauffer VL, et al. Effect of galcanezumab on severity and symptoms of migraine in phase 3 trials in patients with episodic or chronic migraine. *Journal of Headache*. 2021;22(1):6. doi:10.1186/s10194-021-01215-9.

28. Alasad YW, Asha MZ. Monoclonal antibodies as a preventive therapy for migraine: A meta-analysis. [Review]. *Clinical Neurology & Neurosurgery*. 2020;1:105900. doi:10.1016/j.clineuro.2020.105900.

29. Deng H, Li G-G, Nie H, et al. Efficacy and safety of calcitonin-gene-related peptide binding monoclonal antibodies for the preventive treatment of episodic migraine - an updated systematic review and meta-analysis. *BMC Neurology*. 2020;20(1):57. doi:10.1186/s12883-020-01633-3.

30. Canadian Agency for Drugs and Technologies in Health. Erenumab (Aimovig) Clinical Review Report. CADTH Common Drug Review. September 2020.

31. Oskoui M, Pringsheim T, Holler-Managan Y, et al. Practice guideline update summary: Acute treatment of migraine in children and adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2019;93(11):487-499. doi:10.1212/WNL.0000000000008095.

32. Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology*. 2020;94(13):e1365-e1377. doi:10.1212/WNL.0000000000009169.

33. Mulleners WM, Kim B-K, Láinez MJA, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. *The Lancet Neurology*. 2020;19(10):814-825. doi:10.1016/S1474-4422(20)30279-9.

34. Winner PK, McAllister P, Chakhava G, et al. Effects of Intravenous Eptinezumab vs Placebo on Headache Pain and Most Bothersome Symptom When Initiated During a Migraine Attack: A Randomized Clinical Trial. *JAMA*. 2021;325(23):2348-2356. doi:10.1001/jama.2021.7665.

Appendix 1: Current Preferred Drug List

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

Appendix 2: Abstracts of Comparative Clinical Trials

Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial

Robert Croop Richard B Lipton , David Kudrow, David A Stock, Lisa Kamen, Charles M Conway, Elyse G Stock, Vladimir Coric, Peter J Goadsby

Abstract

Background: Rimegepant is a calcitonin gene-related peptide receptor antagonist that has shown efficacy and safety in the acute treatment of migraine. We aimed to compare the efficacy of rimegepant with placebo for preventive treatment of migraine.

Methods: We did a multicentre, phase 2/3, randomised, double-blind, placebo-controlled trial at 92 sites in the USA. Adults with at least a 1-year history of migraine were recruited. After a 4-week observation period, eligible participants were randomised using an interactive web response system to oral rimegepant 75 mg or matching placebo every other day for 12 weeks (double-blind treatment phase). The primary efficacy endpoint was change from the 4-week observation period in the mean number of migraine days per month in the last 4 weeks of the double-blind treatment phase (weeks 9-12). Participants who received at least one dose of their assigned study medication and who had 14 days or more of data in the observation period and 14 days or more of data for at least one 4-week interval during the double-blind treatment phase were analysed for efficacy. Those who received at least one dose of study medication were analysed for safety. This study is registered with ClinicalTrials.gov, NCT03732638.

Findings: Between Nov 14, 2018, and Aug 30, 2019, 1591 participants were recruited and assessed for eligibility, of whom 747 were randomly allocated either rimegepant (n=373) or placebo (n=374). 695 participants were included in the analysis for efficacy, of whom 348 were assigned rimegepant and 347 were allocated placebo. Rimegepant was superior to placebo on the primary endpoint of change in the mean number of migraine days per month during weeks 9-12. The change from the observation period in mean number of migraine days per month during weeks 9-12 was -4·3 days (95% CI -4·8 to -3·9) with rimegepant and -3·5 days (-4·0 to -3·0) with placebo (least squares mean difference -0·8 days, 95% CI -1·46 to -0·20; p=0·0099). 741 participants received study medication and were included in the safety analysis. 133 (36%) of 370 patients who received rimegepant reported an adverse event, compared with 133 (36%) of 371 who received placebo. Seven (2%) participants who received rimegepant and four (1%) who received placebo discontinued the study due to an adverse event; no patients died.

Interpretation: Taken every other day, rimegepant was effective for preventive treatment of migraine. Tolerability was similar to that of placebo, and no unexpected or serious safety issues were noted.

Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2

Richard B Lipton, Peter J Goadsby, Jeff Smith, Barbara A Schaeffler, David M Biondi, Joe Hirman, Susan Pederson, Brent Allan, Roger Cady

Abstract

Objective: To evaluate the efficacy and safety of eptinezumab, a humanized anti-calcitonin gene-related peptide monoclonal antibody, in the preventive treatment of chronic migraine (CM).

Methods: The Prevention of Migraine via Intravenous ALD403 Safety and Efficacy-2 (PROMISE-2) study was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Adults with CM were randomly assigned to receive IV eptinezumab 100 mg, eptinezumab 300 mg, or placebo administered on day 0 and week 12. The primary endpoint was change from baseline in mean monthly migraine days (MMDs) over weeks 1 to 12.

Results: Among treated participants (n = 1,072), baseline mean number of MMDs was ≈16.1 across groups. Treatment with eptinezumab 100 and 300 mg was associated with significant reductions in MMDs across weeks 1 to 12 compared with placebo (placebo -5.6, 100 mg -7.7, $p < 0.0001$ vs placebo; 300 mg -8.2, $p < 0.0001$ vs placebo). Treatment-emergent adverse events (TEAEs) were reported by 43.5% (100 mg), 52.0% (300 mg), and 46.7% (placebo) of patients. Nasopharyngitis was the only TEAE reported for >2% of eptinezumab-treated patients at an incidence of >2% over placebo; it occurred in the 300 mg eptinezumab arm (eptinezumab 9.4%, placebo 6.0%).

Conclusion: In patients with CM, eptinezumab 100 and 300 mg was associated with a significant reduction in MMDs from the day after IV administration through week 12, was well tolerated, and demonstrated an acceptable safety profile.
Classification of evidence: This study provides Class I evidence that for patients with CM, a single dose of eptinezumab reduces MMDs over 12 weeks of treatment.

Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial

Wim M Mulleners, Byung-Kun Kim, Miguel J A Láinez, Michel Lanteri-Minet, Patricia Pozo-Rosich, Shufang Wang, Antje Tockhorn-Heidenreich, Sheena K Aurora, Russell M Nichols, Laura Yunes-Medina, Holland C Detke

Abstract

Background: Many patients who require migraine preventive treatment have not been able to tolerate or have not responded to multiple previous preventive medications. We aimed to assess the safety and efficacy of galcanezumab, an antibody to calcitonin gene-related peptide, in patients with migraine who had not benefited from preventive medications from two to four categories.
Methods: CONQUER was a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial done at 64 sites (hospitals, clinics, or research centres) in 12 countries (Belgium, Canada, Czech Republic, France, Germany, Hungary, Japan, the Netherlands, South Korea, Spain, the UK, and the USA). Patients were 18-75 years of age, with episodic or chronic migraine, with migraine onset before the age of 50 years, who had a documented failure of preventive medications from two to four drug categories in the past 10 years owing to lack of efficacy or tolerability, or both. Patients were randomised 1:1 to receive subcutaneous placebo or galcanezumab 120 mg per month (with a 240 mg loading dose administered as two 120 mg injections) for 3 months. For masking purposes, patients receiving placebo also received two injections during the first dosing visit. Randomisation was done by a computer-generated random sequence by means of an interactive web-response system stratified by country and migraine frequency (low frequency episodic migraine, four to fewer than eight migraine headache days per month; high frequency episodic migraine, eight to 14 migraine headache days per month and fewer than 15 headache days per month; chronic migraine, at least eight migraine headache days per month and at least 15 headache days per month). The primary endpoint was the overall mean change from baseline in number of monthly migraine headache days during the 3-month treatment period in all patients who were randomly assigned and received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT03559257, and is now completed.
Findings: Between Sept 10, 2018, and March 21, 2019, 462 participants with episodic (269 [58%]) or chronic (193 [42%]) migraine were randomly assigned and received at least one injection with placebo (n=230) or galcanezumab (n=232). Galcanezumab-treated patients had significantly greater reduction in migraine headache days versus placebo across months 1-3. The galcanezumab group had on average 4·1 fewer monthly migraine headache days compared with baseline (13·4), while the placebo group had on average 1·0 fewer than at baseline (13·0; between-group difference -3·1 [95% CI -3·9 to -2·3]; p<0·0001; effect size=0·72). Types and number of treatment-emergent adverse events were similar between galcanezumab and placebo. Treatment-emergent adverse events were reported in 122 (53%) of 230 patients in the placebo group and 119 (51%) of 232 patients in the galcanezumab group. There were four serious adverse events during the study, two (1%) reported in the placebo group and two (1%) reported in the galcanezumab group.
Interpretation: Galcanezumab was superior to placebo in the preventive treatment of migraine and was safe and well tolerated in patients for whom multiple previous standard-of-care preventive treatments had failed. Galcanezumab might represent an important treatment option for patients who have not benefited from or tolerated previous standard-of-care treatments.

Effects of Intravenous Eptinezumab vs Placebo on Headache Pain and Most Bothersome Symptom When Initiated During a Migraine Attack: A Randomized Clinical Trial

Paul K Winner, Peter McAllister [6], George Chakhava [7], Jessica Ailani [8], Anders Ettrup [9], Mette Krog Josiassen [9], Annika Lindsten [9], Lahar Mehta [10], Roger Cady [11]

Abstract

Importance: Intravenous eptinezumab, an anti-calcitonin gene-related peptide antibody, is approved for migraine prevention in adults. It has established onset of preventive efficacy on day 1 after infusion.

Objective: To evaluate the efficacy of and adverse events related to eptinezumab when initiated during a migraine attack.

Design, setting, and participants: Phase 3, multicenter, parallel-group, double-blind, randomized, placebo-controlled trial conducted from November 4, 2019, to July 8, 2020, at 47 sites in the United States and the country of Georgia. Participants (aged 18-75 years) with a greater than 1-year history of migraine and migraine on 4 to 15 days per month in the 3 months prior to screening were treated during a moderate to severe migraine attack.

Interventions: Eptinezumab, 100 mg (n = 238), or placebo (n = 242), administered intravenously within 1 to 6 hours of onset of a qualifying moderate to severe migraine.

Main outcomes and measures: Co-primary efficacy end points were time to headache pain freedom and time to absence of most bothersome symptom (nausea, photophobia, or phonophobia). Key secondary end points were headache pain freedom and absence of most bothersome symptom at 2 hours after start of infusion. Additional secondary end points were headache pain freedom and absence of most bothersome symptom at 4 hours and use of rescue medication within 24 hours.

Results: Of 480 randomized and treated patients (mean age, 44 years; 84% female), 476 completed the study. Patients treated with eptinezumab vs placebo, respectively, achieved statistically significantly faster headache pain freedom (median, 4 hours vs 9 hours; hazard ratio, 1.54 [P < .001]) and absence of most bothersome symptom (median, 2 hours vs 3 hours; hazard ratio, 1.75 [P < .001]). At 2 hours after infusion, in the respective eptinezumab and placebo groups, headache pain freedom was achieved by 23.5% and 12.0% (between-group difference, 11.6% [95% CI, 4.78%-18.31%]; odds ratio, 2.27 [95% CI, 1.39-3.72]; P < .001) and absence of most bothersome symptom by 55.5% and 35.8% (between-group difference, 19.6% [95% CI, 10.87%-28.39%]; odds ratio, 2.25 [95% CI, 1.55-3.25]; P < .001). Results remained statistically significant at 4 hours after infusion. Statistically significantly fewer eptinezumab-treated patients used rescue medication within 24 hours than did placebo patients (31.5% vs 59.9%, respectively; between-group difference, -28.4% [95% CI, -36.95% to -19.86%]; odds ratio, 0.31 [95% CI, 0.21-0.45]; P < .001). Treatment-emergent adverse events occurred in 10.9% of the eptinezumab group and 10.3% of the placebo group; the most common was hypersensitivity (eptinezumab, 2.1%; placebo, 0%). No treatment-emergent serious adverse events occurred.

Conclusions and relevance: Among patients eligible for preventive migraine therapy experiencing a moderate to severe migraine attack, treatment with intravenous eptinezumab vs placebo shortened time to headache and symptom resolution. Feasibility of administering eptinezumab treatment during a migraine attack and comparison with alternative treatments remain to be established.

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to July 07, 2021
Search Strategy:

#	Searches	Results
1	eptinezumab.mp.	83
2	erenumab.mp.	267
3	fremanezumab.mp.	162
4	galcanezumab.mp.	193
5	rimegepant.mp.	77
6	ubrogepant.mp.	83
7	1 or 2 or 3 or 4 or 5 or 6	567
8	limit 7 to (english language and humans and yr="2020 -Current" and (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review"))	38

Appendix 4: Key Inclusion Criteria

Population	Patients with migraine (with and without aura)
Intervention	CGRP antagonists
Comparator	Placebo or active control
Outcomes	Number of migraines per month, time to pain freedom
Timing	Acute (abortive treatment) and preventative therapy
Setting	Outpatient

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 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
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

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 (abortive) migraine treatment AND the patient is an adult (18 years or older)?	**Yes:** Go to #13	**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 #16	**No:** Go to #9
9. 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 # 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. Is the request for erenumab and the patient has pre-exisitng hypertension or risk factors for hypertension?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #12
12. 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
13. In a patient with acute migraines, has the patient failed adequate trials of abortive therapy (2 or more different triptans) or have contraindications to triptans?	**Yes:** Go to #14	**No:** Pass to RPh. Deny; medical appropriateness. Recommend triptan trial.
14. Does the patient have chronic migraines?	**Yes**: Go to #15	**No**: Approve for 3 months
15. 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

Approval Criteria		
16. Has the patient failed at least 2 cluster headache preventative treatments (i.e., lithium, verapamil, melatonin, prednisone, subocciptal 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 reponse, 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: 10/21 (KS), 8/20 (KS); 5/19; 9/18 (DE)
Implementation: 1/1/2022; 11/1/2018