INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *CGRPs and 5HT$_{1F}$ Agonists*
-January 2024-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of migraine agents with a primary focus on the calcitonin gene-related peptides (CGRPs) and 5HT$_{1F}$ agonists. The IHS National Core Formulary (NCF) does not contain any of these agents. A review of acute migraine treatments and chronic migraine treatments was completed in 2021 and 2019, respectively. This review encompassed agents not included in the previous reviews and updated literature. Following clinical review and analysis, the NPTC made **no modifications** to the NCF.

Migraines are one of the most common complaints to neurologists and a common reason for emergency room visits.[1] They are ranked 2nd after low back pain worldwide among all diseases with respect to years of life lived with disability.[2,3] Roughly 15% of the population suffers from migraines, and attacks can last 4 - 72 hours. Despite migraine prevalence remaining stable at ~16%, American Indian/Alaska Natives have the highest prevalence at 22%.[2,3] The pathophysiology of migraines is not well understood but theories support the role of inflammation and pain in migraine attacks.[1,4] Common precipitating and exacerbating factors include stress, menstruation, hormone fluctuation, fasting, and weather changes.[5] The goal of migraine management is pain relief/freedom at 2 and 24 hours and a reduction in the number of monthly migraine days.[1]

Discussion:

Although not discussed in this review, triptans (5HT$_1$) remain the gold standard of acute migraine treatment and are available on the NCF.[1] Triptans are thought to act peripherally causing vasoconstriction, and as a result, are contraindicated in cardiovascular disease. Few trials have compared the triptans head-to-head; however, a meta-analysis looking at oral triptans concluded all agents were effective and well tolerated but the most effective agents were rizatriptan (10mg), eletriptan (80mg), and almotriptan (12.5mg).[1] Ditans, which selectively target the 5HT$_{1F}$ receptor, are useful when triptans are contraindicated because they inhibit CGRP release, which is associated with migraine attacks, but are not mediated through vasoconstriction and do not have cardiac adverse effects (AE).[1] The only FDA-approved medication in this class is lasmiditan, an oral acute migraine option dosed once daily with warnings for CNS depression[1].

The CGRP is a vasodilator neuropeptide that is elevated during migraines. The CGRP drug class contains two types of agents, the “gepants” (ubrogepant, rimegepant, atogepant, zavegepant) which act as a CGRP receptor blocker, and the monoclonal antibodies (erenumab, fremanezumab, galcanezumab, eptinezumab), which block CGRP itself.[1] This class can be used for both acute and preventive treatment.[1,6] Monoclonal antibodies (mAbs) target either CGRP or the receptor and are used for prevention. They are given subcutaneously, take longer to start working, but have fewer drug interactions. Since the last review, eptinezumab has come to market. Gepants are effective for both acute and chronic treatment. Gepants work quickly but are metabolized in the liver and have a higher potential for drug interactions and liver damage. These agents are available in oral or nasal formulations. Since the last review, atogepant and zavegepant have come to market.[1,6]

The 2019 European Headache Federation: Management of Headache Disorders guidelines recommend triptans for acute attacks and do not address the use of 5HT$_{1F}$ or CGRPs.[7] For prevention, the guidelines do not incorporate CGRPs until 7th line. These guidelines do not give preference to one agent within a class over another.[7] The 2022 European Headache Federation: CGRP Monoclonal Antibodies for Prevention guidelines provide recommendations for the use of any approved CGRP mAb.[8] The 2021 American Headache Society Consensus Statement: Integration of New Migraine Treatment guidelines recommend using migraine-specific agents for moderate to severe attacks or mild attacks that do not respond well to nonspecific therapy. They list both CGRPs and the 5HT$_{1F}$, among other agents, but do not give preference and recommend agent selection be made based on clinical experience and individual patient factors.[9] In regard to prevention, the guidelines list CGRP mAbs but do not give preference to this class over others.[9] Many of these guidelines also recommend certain criteria be met before trying these agents and in consultation with a specialist.[7-9] The 2023 VA/DoD Clinical Practice Guideline: Management of Headache guidelines have weak recommendations for the use of rimegepant and ubrogepant for acute treatment and do not lean either way for the use of lasmiditan.[10] When evaluating preventative options, the guidelines have strong recommendations for the use of erenumab, fremanezumab, or galcanezumab; a neutral stance on the use of rimegepant; and weak recommendations for the use of eptinezumab and atogepant.[10]

A 2022 study reviewing the safety and efficacy of atogepant (10mg, 30mg, 60mg) in adult migraine prevention reported a significant reduction in monthly migraines (p<0.00001, p<0.00001, p=0.007), headaches (p<0.00001, p<0.00001, p=0.001), and medication use days (p<0.00001, p<0.00001, p=0.0001) compared to placebo and an increase in those with a >50% reduction in monthly migraine days (p=0.0008, p=0.02, p=0.04). No major differences were noted in adverse effects between agents (p>0.05).[11] A 2023 clinical trial evaluating the safety and efficacy of nasal zavegepant in adult migraine treatment against other nasal agents found zolmitriptan 5mg was most effective for pain freedom at 2 hours (OR: 4.64, 95% CI: 3.51

to 6.123; *p*<0.0001) and 24 hours (OR: 5.49, 95% CI: 3.58-8.42; p<0.0001).[12] Dihydroergotamine had the highest risk of AEs (OR: 9.65, 95% CI: 4.39-21.22; *p*<0.0001) whereas zavegepant had the lowest risk of AEs (OR: 2.04, 95% CI: 1.37-3.03; *p*=0.0005). A study looking at safety and tolerability of eptinezumab for adult migraine prevention showed a safe and tolerable drug profile and overall adverse effects did not differ greatly between doses.[13]

A 2021 systematic review and meta-analysis of acute treatments including ergots, triptans, gepants, and $5HT_{1F}$ found that triptans had higher odds ratios (OR) of 2-hour pain freedom versus lasmiditan (range: OR 1.72 [95% CI: 1.06-2.80] to OR 3.40 [95% CI: 2.12-5.44]), rimegepant (range: OR 1.58 [95% CI: 1.07-2.33] to OR 3.13 [95% CI: 2.16-4.52]), and ubrogepant (range: OR 1.54 [95% CI: 1.00-2.37] to OR 3.05 [95% CI: 2.02-4.60])[14]. Comparisons between lasmiditan, rimegepant, and ubrogepant were not statistically significant for either pain freedom and pain relief at 2 hours. Rizatriptan (OR 1.96, 95% CI: 1.14-3.35), sumatriptan (OR 1.83, 95% CI: 1.09-3.09), and zolmitriptan (OR 2.34, 95% CI: 1.39-3.95) were associated with a higher risk of any AE compared to CGRPs[14].

A network meta-analysis comparing the safety and efficacy of mAb CGRPs showed that all mAb CGRPs were more effective than placebo in migraine prevention.[15] Monthly fremanezumab 225mg had the greatest reduction in migraine days (SMD= -0.49, 95% CI: -0.62 to -0.37) and >50% response rate (RR=2.98, 95% CI: 2.16-4.10) while erenumab 140 mg had the largest reduction in acute medication days (SMD= -0.68, 95% CI: -0.79 to -0.58) and galcanezumab 240mg and quarterly fremanezumab 675mg had the highest AE rates[15].

A systematic review and meta-analysis from 2023 compared the effectiveness of migraine prevention from antidepressants, antiepileptics, antihypertensives, CGRP mAb, and CGRP gepants.[16] The study found CGRPs (mAb and gepants) and topiramate demonstrated significant reductions of ≥50% in migraine days compared to placebo, with fremanezumab showing the greatest reduction (RR 2.24, 95% CI: 1.80-2.79). Other commonly used drug classes like beta blockers, amitriptyline, and valproate showed a moderate decrease. The highest risk of discontinuation due to AEs was with valproate and amitriptyline. Notably, the CGRP subclasses did not show an increased AE risk.

Clinical trials are ongoing for both CGRPs and $5HT_{1F}$ agonists. Many of these agents are enrolling or actively participating in clinical trials to expand use in pediatrics and pregnancy populations, along with the expansion of migraine indications.[17]

Findings:

Migraines are a common yet debilitating condition and the pathophysiology is not completely understood. Triptans remain the gold standard for acute treatment but newer classes of medications have shown to be safe and effective for both the treatment and prevention of migraines. Both CGRPs and ditans are currently recommended as 2nd or 3rd line therapies in guidelines and are not recommended until multiple treatment failures have occurred with different medication classes. Ultimately, treatment selection should be focused on patient-specific factors, history, and AE profiles.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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