



Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: Acute Migraine
-January 2021-



Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) reviewed acute migraine treatment at the January 2021 meeting. Recently, three novel medications from two classes (“ditan” and “gepants”) were approved by the FDA. The comparative efficacy and tolerability of these medications compared to the triptans was the main focus of this review. In 2016, the NPTC reviewed and named triptans to the National Core Formulary, stating that any two “triptans” could be added, but that one of the two triptan medications must be sumatriptan. At the conclusion of the review, the NPTC made no modifications to the National Core Formulary.

Discussion:

Migraine is common in the United States. One out of every six Americans (1 out of 5 women) will have a migraine over a 3-month period. In 2015, migraine prevalence was highest in American Indians or Alaska Natives compared to other races at 18.4%. There is a higher burden of migraine in persons aged 18-44 (17.9%), in those who are unemployed (21.4%), and in those with family incomes less than \$35,000 per year (19.9%).¹ Migraine has been classified as the second most disabling disorder worldwide.²

Pathophysiology of migraine is not fully understood; however, it does appear to involve the activation of the trigeminovascular system to cause cranial vasodilation. It was also discovered that infusions of calcitonin-gene related peptide (CGRP) caused migraine-like headaches.² As a result, CGRP and its associated receptors became a target of acute migraine medication therapy.

The treatment goals often associated with acute migraine are pain relief or freedom from pain at 2 hours and 24 hours. Triptan medications are the mainstay of acute migraine treatment. Triptans cause vasoconstriction via activation of the 5-HT_{1B} receptor. Although they have selective affinity for cranial vessels, they can also target cardiovascular blood vessels. Triptans also decrease plasma levels of CGRP, which is a probable mechanism of action. Triptans are contraindicated in patients with known cardiovascular disease. A meta-analysis of 133 randomized controlled trials (RCTs) studying the efficacy and tolerability of triptans showed that triptans provided headache relief within 2 hours in 43-76% of patients. Additionally, freedom from pain was reported within 2 hours for 18-50% of participants, as was sustained headache relief at 24 hours in 29-50% of patients, and sustained freedom from pain at 24 hours for 18-33% of patients.⁴

Although triptans are effective for many patients, even the most efficacious triptan may not work for all patients. Also, triptans may cause undesirable side effects in some patients, resulting in poor adherence. Recently, new medications with novel mechanisms were approved for the acute treatment of migraine headaches in adults.

Lasmiditan received FDA approval in October 2019 and is the first medication approved in the novel “ditan” class. Lasmiditan is a 5-HT_{1F} selective agonist and has much lower affinity for the 5-HT_{1B} receptor as compared to triptans. As a result, it does not cause vasoconstriction in coronary arteries and can be used in patients with cardiovascular disease.¹ However, drawbacks of lasmiditan include CNS adverse effects, its status as a controlled substance (C-V), and the following warning contained within the package insert, “Do not administer lasmiditan unless patient can wait at least 8 hours between dosing and operating heavy machinery or driving.”⁵

A meta-analysis of 4 RCTs was conducted to examine the efficacy and tolerability of lasmiditan. The authors found that lasmiditan is more effective than placebo in providing pain freedom at 2 hours post dose with a risk ratio (RR) of 1.71 (1.55-1.87). Lasmiditan was also more effective at providing pain relief at 2 hours with a risk ratio of 1.4 (1.33-1.47). Lasmiditan reportedly had more adverse effects compared to placebo; RR dizziness: 5.81 (4.71-7.14), RR nausea: 2.58 (1.87-3.57), RR fatigue: 5.38 (3.78-7.66), RR paresthesia: 4.48 (3.33-6.02), and RR somnolence: 2.82 (2.18-3.66).⁶

The FDA recently approved two new medications for the treatment of acute migraine in the novel “gepant” class. Ubrogepant was approved in December 2019 and rimegepant was approved in February 2020. These

medications are small-molecule CGRP receptor antagonists and are structurally different from the currently approved and larger-molecule CGRP receptor antagonists (i.e., erenumab, fremanezumab, galcanezumab, eptinezumab) which are monoclonal antibodies.² The NPTC previously reviewed this medication class in [November 2019](#).

A meta-analysis published in 2020 of 4 RCTs was conducted to assess the efficacy and safety of rimegepant. Rimegepant was found to be more effective than placebo in providing freedom from pain 2 hours post dose (RR 1.7; 1.39-2.08), freedom from most bothersome symptom (RR 1.44; 1.23-1.68), and pain relief 2 hours post dose (RR 1.34; 1.25-1.44). Rimegepant was not associated with an increase of side effects compared to placebo.⁷

Gao et al. conducted a meta-analysis of 3 RCTs in 2020 to assess the efficacy and tolerability of ubrogepant. Ubrogepant was found to be more effective than placebo in all study areas including freedom from pain 2 hours post dose (RR 1.65; 1.38-1.98), absence of the most bothersome symptom (RR 1.35; 1.2-1.53), and pain relief at 2 hours post dose (RR 1.26; 1.17-1.36). Ubrogepant was not associated with an increase of side effects compared to placebo.⁸

Due to limited comparative data and the absence of true head-to-head trials between triptans and the newer agents, the Institute for Clinical and Economic Review (ICER) conducted a network meta-analysis to compare the newer agents to sumatriptan (most widely used triptan) and eletriptan (most efficacious and best tolerated triptan). The authors concluded that triptans continue to be most cost-effective agents for the treatment of acute migraines. Rimegepant and ubrogepant were considered cost-effective alternatives for patients who fail triptans or have contraindications. Although lasmiditan was found to be equally efficacious to the gepants in the ICER comparison, it did not cross the threshold considered to indicate cost effectiveness.³

Findings:

Migraine is associated with significant morbidity. American Indians and Alaska Natives have the highest prevalence of migraine headaches among all races in the United States.^{1,2} Triptans are effective for acute migraine and continue to be considered the gold standard for treatment. However, some patients with migraines are unable to take triptans due to side effects or contraindications. Ubrogepant, rimegepant, and lasmiditan are effective alternatives to triptans, although external analyses indicate that lasmiditan has not been determined to be cost effective at this time.³

Although gepants are considered to be potentially cost effective alternatives to triptans, there is limited data to support their use. As such, they are not widely included or universally recommended in national guidelines for migraines. Additionally, internal indices report extremely limited usage across the agency. Accordingly, the NPTC made no modifications to the National Core Formulary at this time.

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](#).

References:

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