New Drug Overview
Reyvow (lasmiditan)

INTRODUCTION

- Migraine is a debilitating neurological disorder characterized by recurring, often unilateral, throbbing headaches of moderate to severe intensity that are exacerbated by physical activity and associated with nausea, vomiting, photophobia, and phonophobia. It is a common condition that affects up to 12% of the general population and is more frequent in women than in men *(American Headache Society [AHS] 2019, Cutrer 2019, Rubio-Beltrán et al 2018*).
  - Migraine attacks typically last between 4 and 72 hours in adults, and usually progress through 4 phases: the prodrome, the aura (occurs in approximately 25% of individuals), the headache, and the postdrome.
    - Factors that may trigger a migraine include stress, menstruation, visual stimuli, weather changes, nitrates, fasting, wine, sleep disturbances, and aspartame, among others.
- Migraine is currently considered a neurovascular disorder that involves activation of the trigeminovascular system, followed by cranial vasodilation mediated by release of signaling proteins including calcitonin gene-related peptide (CGRP) *(Rubio-Beltrán et al 2018*).
- Prescription drugs for acute migraine treatment include triptans, dihydroergotamine (DHE), and non-steroidal anti-inflammatory drugs (NSAIDs) which can be used alone or in combination with a triptan. All 3 drug classes have restrictions regarding use in patients with cardiovascular disease (CVD) (*Reyvow U.S. Food and Drug Administration [FDA] Summary Review 2019*, *Smith 2019*).
  - First line treatment options include analgesics (eg, NSAIDs, acetaminophen [APAP]) or combination analgesics for mild to moderate attacks not associated with vomiting or nausea. For patients with moderate to severe attacks, oral migraine-specific agents such as triptans are first-line.
- New therapeutic classes for acute treatment of migraine attacks include CGRP antagonists and 5-hydroxytryptamine (5-HT)$_{1F}$ receptor agonists.
  - Reyvow (lasmiditan) was approved in October 2019; it is the first FDA-approved medication in a new class of 5-HT$_{1F}$ receptor agonists, also referred to as “ditans.”
- Lasmiditan binds with high affinity to the 5-HT$_{1F}$ receptor and presumably exerts its therapeutic effects in the treatment of migraine through agonist effects at the 5-HT$_{1F}$ receptor; however, the precise mechanism is unknown (*Reyvow Prescribing Information 2020*).
- Medispan class: Migraine Agents; Serotonin Agonists; Selective Serotonin Agonists (5-HT$_{1F}$)

INDICATION

- Lasmiditan is indicated for the acute treatment of migraine with or without aura in adults.
  - Limitations of use: Lasmiditan is not indicated for the preventive treatment of migraine.
- Information on the indication, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the product, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The efficacy of lasmiditan in the acute treatment of migraine with or without aura was demonstrated in two Phase 3, double-blind (DB), randomized, placebo-controlled (PC) trials (SAMURAI, *Kuca et al 2018* and SPARTAN, *Goadsby et al 2019*). A total of 3177 adult patients received lasmiditan 50 mg, 100 mg, or 200 mg. Both studies included patients with cardiovascular (CV) risk factors, but only SPARTAN included patients with known coronary artery disease (CAD), clinically significant arrhythmia, or uncontrolled hypertension. The efficacy of lasmiditan was evaluated in terms of pain freedom (defined as a reduction of moderate or severe headache pain to no pain) and Most Bothersome Symptom (MBS) freedom (defined as the absence of the self-identified MBS [photophobia, phonophobia, or nausea]) at 2 hours compared to placebo (*Reyvow Prescribing Information 2020*).
  - In both studies, the percentage of patients achieving pain freedom and MBS freedom 2 hours after treatment was significantly greater among patients receiving lasmiditan at all doses compared to those receiving placebo (see Table 1) (*Reyvow FDA Summary Review 2019*, *Reyvow Prescribing Information 2020*).

- The treatment effect size for pain freedom at 2 hours post-dose was approximately 7% to 18% greater than placebo across the 3 doses tested.
- The treatment effect size for MBS-freedom at 2 hours was approximately 8% to 16% greater than placebo across the 3 doses tested.

○ Pain relief at 2 hours, defined as a reduction in migraine pain from moderate or severe to mild or none, was also evaluated (see Table 1).

Table 1. Results for key migraine efficacy endpoints

	SAMURAI			SPARTAN			
	Lasmiditan 100 mg	Lasmiditan 200 mg	Placebo	Lasmiditan 50 mg	Lasmiditan 100 mg	Lasmiditan 200 mg	Placebo
Pain free at 2 hours							
N	498	503	515	544	523	521	534
% responders	28.3	31.8	15.3	28.3	31.4	38.8	21.0
Difference from placebo (%)	13	16.5	--	7.3	10.4	17.8	--
p-value	< 0.001	< 0.001	--	0.006	< 0.001	< 0.001	--
MBS free at 2 hours							
N	464	467	480	502	491	478	509
% responders	41.2	40.7	29.6	40.8	44.0	48.7	33.2
Difference from placebo (%)	11.6	11.1	--	7.6	10.8	15.5	--
p-value	< 0.001	< 0.001	--	0.014	< 0.001	< 0.001	--
Pain relief at 2 hours*							
N	498	503	515	544	523	521	534
% responders	54.0	55.3	40.0	55.9	61.4	61.0	45.1
Difference from placebo (%)	14.0	15.3	--	10.8	16.3	15.9	--
*The analysis of pain relief was descriptive and as not controlled for Type I error							

○ In both trials, the most common adverse events (AEs) were dizziness, fatigue, lethargy, nausea, paresthesia, and somnolence. No serious treatment-emergent adverse events (TEAEs) related to study drug were reported in SAMURAI, while 2 serious AEs considered to be treatment-related were reported in SPARTAN (100 mg, dystonic reaction; 200 mg, presyncope).

- The rate of serious AEs with a potential CV etiology was low. The most commonly reported CV TEAEs in the controlled trials were palpitations/heart rate increased/tachycardia occurring in 0.4% of patients on lasmiditan and 0.1% on placebo.

- The open-label (OL) extension trial GLADIATOR (*Brandes et al 2019*) randomized patients from the SAMURAI and SPARTAN trials to receive lasmiditan 100 mg or 200 mg. The goal was to evaluate the safety and efficacy of long-term intermittent use of lasmiditan for the acute treatment of migraine for up to 1 year. Of the 2116 patients who were randomized, 1978 patients received ≥ 1 dose of lasmiditan (safety population) and treated 19,058 migraine attacks. At the time of the data cut-off for the interim analysis, 814 (41.2%) patients in the safety population had completed all 12 months of the study, and 141 (7.1%) patients were continuing treatment. The median duration of time in the study was 288 days.
  - ○ A total of 962 patients (48.6%) reported ≥ 1 TEAE during the study. Frequently reported TEAEs were similar to those in the pivotal trials and included dizziness (18.6%), somnolence (8.5%), and paresthesia (6.8%). Dizziness was the most common AE leading to discontinuation.
  - ○ No CV TEAEs potentially due to vasoconstriction were observed. No treatment-emergent serious AE was considered by the investigator to be related to lasmiditan. No deaths were reported during the study.
  - ○ Overall, across all treated attacks at 2 hours post-dose, pain freedom was observed in 29.6% of attacks, MBS freedom in 39.0%, and pain relief in 56.3%, with significantly higher percentages observed in the 200 mg group than in the 100 mg group ($p < 0.001$ for all comparisons).
- Analyses evaluating the safety and efficacy of a second lasmiditan dose when taken for rescue or recurrence found some evidence of efficacy when taken for headache recurrence, but there was no clear benefit of a second dose for rescue treatment (*Loo et al 2019*). However, due to shortcomings with the analyses, the FDA did not consider the data

to be informative and did not consider efficacy of the second dose to be established. Thus, the lasmiditan label only recommends that a single dose of lasmiditan be taken in a 24-hour period (*Reyvow FDA Summary Review 2019).*

- An Institute for Clinical and Economic Review (ICER) network meta-analysis (*Atlas et al 2020*) of 33 randomized controlled trials (RCTs) was conducted to compare the safety and efficacy of lasmiditan and the oral CGRP antagonists, rimegepant and ubrogepant, for acute treatment of migraine to each other, placebo, and triptans.
  - Lasmiditan, rimegepant, and ubrogepant all had higher odds of achieving pain freedom and pain relief at 2 hours vs placebo. Compared to each other, none of these interventions showed statistically significant differences, although lasmiditan showed statistically nonsignificant higher odds of achieving pain freedom. All interventions showed lower odds of achieving pain freedom compared to eletriptan and sumatriptan, but statistical significance was not reached for lasmiditan vs sumatriptan. Similar trends were observed for pain relief at 2 hours.
  - Lasmiditan and the CGRP antagonists all had higher odds of achieving freedom from MBS at 2 hours post-dose compared to placebo. Compared to each other, none of the interventions showed a statistically significant difference. None of the triptan studies assessed this outcome.
  - The ICER ratings on the net comparative health benefit of lasmiditan vs comparators for various populations are as follows:
    - For adults who have failed non-prescription drugs and who have failed or are contraindicated to triptans, the evidence for lasmiditan compared to placebo was considered to be “B+”, meaning there’s a moderate certainty of a small or substantial health benefit, with a high certainty of at least a small net health benefit.
    - For patients who have failed non-prescription drugs and are eligible for triptans, lasmiditan was rated a “C-“ vs triptans, meaning that there is moderate certainty that the comparative net health benefit is either comparable or inferior. Results of the meta-analysis suggest that lasmiditan is less efficacious than triptans, although they do not exclude comparable efficacy compared to sumatriptan. However, there is a higher incidence of AEs with lasmiditan compared to triptans.
    - Results of the analysis suggest that lasmiditan may be slightly more efficacious than rimegepant and ubrogepant, but they do not exclude comparable efficacy. However, any possible greater efficacy is at best balanced by the higher incidence of adverse events and may be outweighed by them; thus, lasmiditan received a “C-“ compared to the oral CGRP antagonists.

CLINICAL GUIDELINES

- The American Headache Society (AHS) guidelines recommend the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate migraine attacks. Migraine-specific agents such as triptans or DHE are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to NSAIDs or caffeinated combinations (*AHS 2019*).
  - The guidelines state that emerging acute treatments for migraine headache such as the CGRP antagonists, ubrogepant and rimegepant, and the selective 5-HT_{1F} receptor agonist, lasmiditan, do not have vasoconstrictive effects; therefore, they may play a role in patients with CV contraindications to triptans. It is recommended that patients be eligible for these newer agents if they have contraindications to the use of triptans or have failed to respond to or tolerate ≥ 2 oral triptans.
- Similar to the AHS guidelines, a number of other guidelines recommend non-opioid analgesics for mild to moderate migraine, and migraine specific-agents (eg, triptans) for moderate to severe migraine (*Mayans and Walling 2018*, *Silberstein 2000*, *Steiner et al 2019*).

SAFETY SUMMARY

- Lasmiditan carries warnings and precautions for the following:
  - Driving impairment: Patients are advised not to drive or operate machinery for at least 8 hours after taking lasmiditan, even if they feel well enough to do so. Patients who cannot follow this advice should not take the drug. Patients may not be able to assess their own driving competence and degree of impairment caused by lasmiditan.
  - Central nervous system (CNS) depression: Lasmiditan causes CNS depression, including dizziness and sedation. It should be used with caution if taken in combination with alcohol or other CNS depressants.
  - Serotonin syndrome: Reactions consistent with serotonin syndrome have been reported in patients taking lasmiditan. Symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular signs (eg, hyperreflexia, incoordination), and/or

gastrointestinal AEs (eg, nausea, vomiting, diarrhea). The drug should be discontinued if serotonin syndrome is suspected.
  - Medication overuse headache (MOH): Overuse of acute migraine drugs (eg, ergotamines, triptans, opioids, or a combination of these drugs for ≥ 10 days per month) may lead to exacerbation of headache. Detoxification of patients may be necessary.
- The most common AEs reported by patients in the clinical trials were dizziness, fatigue, paresthesia, sedation, nausea and/or vomiting, and muscle weakness.
  - Lasmiditan was associated with decreases in heart rate and small transient increases in blood pressure. Although the clinical trials enrolled many patients with CV risk factors, only a small percentage of patients (1%) had ischemic heart disease, thus limiting the assessment of lasmiditan's safety in these patients. According to the FDA, the data do not support the need for CV restrictions with the use of lasmiditan; however, they are too limited to definitively establish the CV safety of the drug (*Reyvow FDA Summary Review 2019*).
- Concomitant use of lasmiditan and P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) substrates should be avoided. Caution is advised when patients are taking lasmiditan in combination with alcohol or other CNS depressants, serotonergic drugs, and heart-rate lowering drugs.
- Lasmiditan is a Schedule V controlled substance (C-V).
  - In a human abuse potential study in recreational poly-drug users, subjects taking lasmiditan reported statistically significantly higher "drug liking" scores vs placebo and statistically significantly lower "drug liking" scores vs alprazolam (C-IV).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Reyvow (lasmiditan)	Tablets	Oral	The recommended dose is 50 mg, 100 mg, or 200 mg taken orally, as needed. No more than one dose should be taken in 24 hours, and lasmiditan should not be taken unless the patient can wait at least 8 hours between dosing and driving or operating machinery	A second dose of lasmiditan has not been shown to be effective for the same migraine attack. The safety of treating an average of more than 4 migraine attacks in a 30-day period has not been established. Lasmiditan may be taken with or without food.

See the current prescribing information for full details

CONCLUSION

- Lasmiditan, the first FDA-approved medication in a new class of 5-HT_{1F} receptor agonists, is indicated for the acute treatment of migraine with or without aura in adults.
  - In 2 DB, PC, RCTs, the percentage of patients achieving pain freedom and MBS freedom 2 hours after treatment was significantly greater among patients receiving lasmiditan at all doses compared to those receiving placebo.
  - Lasmiditan has not been compared to other acute migraine treatments such as triptans or oral CGRP antagonists in head-to-head trials.
  - Results of a network meta-analysis evaluating lasmiditan, triptans (sumatriptan and eletriptan), and oral CGRP antagonists (rimegepant, ubrogepant) suggest that lasmiditan is less efficacious than triptans but do not exclude comparable efficacy compared to sumatriptan; however, there is a higher incidence of AEs with lasmiditan compared to triptans. Results also suggest that lasmiditan may be slightly more efficacious than rimegepant and ubrogepant, but they do not exclude comparable efficacy; however, any possible greater efficacy of lasmiditan is at best balanced by the higher incidence of AEs and may be outweighed by them.
- Various clinical guidelines recommend non-opioid analgesics for mild to moderate migraine attacks and migraine specific-agents (eg, triptans) for moderate to severe attacks. According to guidelines from the AHS, newer acute

treatments for migraine such as lasmiditan may play a role in patients who have failed, have contraindications to, or who cannot tolerate triptans.

- Lasmiditan has warnings for CNS depression, serotonin syndrome, MOH, and driving impairment. Patients should not engage in potentially hazardous activities such as driving for at least 8 hours after each dose of the drug. Common AEs reported in the clinical trials included dizziness, fatigue, paresthesia, and sedation. Lasmiditan is a Schedule V controlled substance.
- Lasmiditan, which has high affinity and selectivity for 5-HT_{1F} receptors and lacks the vasoconstrictor activity associated with triptans and ergotamines, may offer an alternative treatment option to some patients. Factors to consider include the abuse potential, the risk of driving impairment for at least 8 hours after each dose, and the restriction to a single dose per 24 hours.

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