Lasmiditan (REYVOW)
National Drug Monograph
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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Lasmiditan is a serotonin (5-HT) 1F receptor agonist. The interaction with 5-HT1F receptors and the absence of vasoconstrictive effects make lasmiditan the first molecule of a new drug category, the neurally acting antimigraine agents.

Indication(s) Under Review in This Document

- Lasmiditan is indicated for the acute treatment of migraine with or without aura in adults.

Dosage Form(s) Under Review

- 50 and 100 mg tablets.

Clinical Evidence Summary[1,2,3,4,5]

Efficacy Considerations[1]

- The clinical trials supporting the safety and efficacy of lasmiditan includes 3 trials[2]: 2 pivotal single-attack placebo-controlled phase 3 studies SAMURAI[3] and SPARTAN[4] and 1 pivotal phase 3 long-term, open-label safety study GLADIATOR[5].
- The efficacy data for these trials are summarized in Table 1

Table 1: Efficacy results from clinical trials

Study	Design	Treatment Arms	Results	
			HA PF at 2 hrs (%)	MBS freedom 2 hrs (%)
SPARTAN[3] (N=2,869)	Phase 3, RCT, DB, MC, PC 8 weeks, history of 3-8 migraine/month Germany, UK, US	L50 L100 L200 placebo	28.6 (p=0.003) 31.4 (p<0.001) 38.8 (p<0.001) 21.3	40.8 44.2 48.7 33.5
SAMURAI[4] (N=2,231)	Phase 3, RCT, DB, MC, PC	L100 L200	28.2 (p,0.001) 32.2 (p<0.001)	40.9 40.7

	8 weeks, history of 3-8 migraine/monTheth US	Placebo	15.3	29.5
GLADIATOR[5] (N=2,116)	phase 3 long-term, open-label safety study			

The approval trials, SAMURI and SPARTAN were conducted in adults diagnosed with migraine with or without aura with a history of 3-8 migraine attacks and less than 15 headache days per month. The SAMURAI study did not include patients with known coronary artery disease, heart rhythm abnormalities, or uncontrolled hypertension. However, the other study, SPARTAN, included this group with heart and vascular disease. The inclusion of this patient group is key, as lasmiditan may provide an alternative to triptan use in this population. It should be noted that, although SPARTAN did include an at-risk population, it was not designed to assess superiority and safety over triptans for this population. The average patient age was 43 years old and females represented 84% of the population in both trials. The mean baseline MIDAS score was 32.2 for the SPARTAN study and 31 for the SAMURAI study, indicating severe disability with both scores above the cutoff of 21.13 Patients with at least one CV risk factor represented 80% patients in the SPARTAN trial and 78% in the SAMURAI trial. Preventative migraine therapy was allowed in both trials; 19% of patients in SPARTAN and 17% of patients in SAMURAI. The primary endpoint for both trials was headache pain-free at 2-hours.

In these pivotal studies, 45% of those participating had used at least 1 triptan; defining then as a triptan-experienced population. Approximately 31% of these triptan users did not demonstrate an acceptable response to these triptans.

In the SPARTAN trial, lasmiditan 200 mg, lasmiditan 100 mg and lasmiditan 50 mg were compared to placebo for the treatment of moderate-to- severe intensity migraine. Time to treatment of attack was similar between all active treatment groups and placebo (approximately 1 hour). Lasmiditan 200 mg was reported to be more effective than placebo with an ARR of 18% and NNT of 6 (OR 2.3; 95% CI, 1.8 to 3.1; P<0.001). Lasmiditan 100 mg and lasmiditan 50 mg were also reported to be more effective than placebo with an ARR of 10% (NNT 10) and 7% (NNT 14), respectively. The co-primary endpoint of freedom from MBS was 48.7% in patients treated with lasmiditan 200mg, 44.2% with lasmiditan 100 mg, 40.8% with lasmiditan 50 mg, and 33.5% for placebo (NNT 7 to 14). For the secondary endpoint of sustained pain freedom at 24 hours, all doses of lasmiditan were statistically different from placebo (ARR 4% to 9%; NNT 11 to 27). Sustained pain freedom at 48 hours was found to be more effective for only the lasmiditan 200 mg group, 19.6% of patients compared to 11.8% of patients in the placebo group (ARR 7.8%; NNT 13). A second dose of medication was used in 21.2% of patients taking lasmiditan 200 mg, 26.3% of patients taking lasmiditan 100 mg, 34.4% of patients taking lasmiditan 50 mg and 39.5% taking placebo. Ninety-five percent of second doses were taken as rescue medication and the rest were for headache recurrence.

In the SAMURAI trial, lasmiditan 200 mg was reported to be more effective than placebo for the primary endpoint, 32.2% and 15.3%, respectively (OR 2.6; 95% CI, 2.0-3.6; P<0.001)(ARR 17.6%/NNT 6).3 Lasmiditan 100mg was found to be associated with freedom of headache pain at 2 hours with an absolute difference from placebo of 12% (NNT 8) (OR 2.2; 95% CI, 1.6 to 3.0; p<0.001). For the secondary endpoint of freedom from the MBS, lasmiditan 200 mg and 100 mg were reported to be more effective than placebo, 40.7%, 40.9% and 29.5% (ARR of 11% and NNT of 9 for both doses). Nineteen percent of patients in the lasmiditan 200 mg group were headache pain free at 24 hours compared to 15% in the 100 mg group and 8% in the placebo group (p<0.001 for both dose comparisons). Freedom from headache pain at 48 hours was also more effective in patients treated with both lasmiditan doses compared to placebo (NNT 12-14).3 Rescue dosing was required in 31.9% of patients taking lasmiditan 200 mg, 39% of patients taking lasmiditan 100 mg, and 59.9% of patients taking placebo. Patients' results were collected up to 7 days after the migraine attack or up to 8 weeks if no attacks were experienced.

GLADIATOR was a long-term (12-month) open-label study conducted to establish the safety of lasmiditan when given to treat multiple migraine attacks. Patients were given either 100 mg or 200 mg of lasmiditan with instructions to use lasmiditan as the first treatment for each new migraine attack within 4 hours of pain onset.20,22 The long-term analysis showed headache days decreased significantly and progressively throughout the year long trial. There was a relatively high dropout rate of 51.7% throughout the trial and 12.8% of patients discontinued the trial due to adverse events.

CENTURION[6] was completed to assess the efficacy and consistency of response to lasmiditan 100 mg or 200 mg across multiple migraine attacks. The duration of the study was the treatment of 4 migraine attacks or 4 months, whichever occurred sooner. Patients were directed to treat their migraine within 4 hours of an attack of moderate to severe intensity and not repeat a dose until more than 48 hours after treatment of an attack to evaluate sustained pain freedom. he efficacy and safety data remained consistent with findings across all the 3 previously conducted Phase III studies.

A network meta-analysis was able to compare data from the acute migraine treatments and utilized 5 different Phase III trials which include SAMURAI and SPARTAN (lasmiditan), ACHIEVE I and ACHIEVE II (ubrogepant), and Study 303 (rimegepant) in order to determine the relative efficacy and adverse effects associated with each acute migraine treatment. The study concluded that rimegepant appeared more efficacious in headache pain freedom compared with placebo and lower doses of lasmiditan and ubrogepant.

Safety Considerations

Safety Results from Clinical Trials:

- CNS adverse events: Lasmiditan is associated with adverse reactions related to dizziness and balance disorder (up to 18%) and somnolence, fatigue and sedation (up to 11%) that occurred with frequency of more than 2% greater than placebo.
- Driving Impairment: A dose-dependent impairment was seen in a simulated driving study 90 minutes after administration of lasmiditan. In a second driving study, mean SDLP did not reach the threshold for driving impairment at 8, 12, and 24 hours after lasmiditan administration. Subjects lacked insight into when they might be impaired to drive based on a Self-Perceived Safety to Drive question.
- Abuse Potential: Treatment-emergent adverse events related to abuse potential in the Phase 3 oral placebo-controlled studies occurred in 28.5% of subjects who received lasmiditan compared to 7.6% of subjects who received placebo.
- Pulse Rate Lowering: Propranolol in combination with lasmiditan 200 mg resulted in a maximum mean decrease in pulse rate of 19.3 beats per minute 1.5 hours after dosing which was a larger decrease at the same time point than lasmiditan 200 mg or propranolol alone. Coadministering lasmiditan with other heart rate lowering drugs may increase the risk of pulse rate lowering.
- Hypersensitivity reactions in the Phase 3 oral placebo-controlled studies occurred in 0.2% of subjects who received lasmiditan compared to 0% of subjects who received placebo.
- Cardiovascular adverse events: Treatment emergent adverse events with potential cardiovascular etiology in the oral Phase 3 placebo-controlled studies occurred in 1.8% of subjects who received lasmiditan compared to 0.5% of subjects who received placebo. The most common events were palpitations and tachycardia.
- The effect of lasmiditan on driving performance was examined in healthy adults. In a driving
- simulator, those who took lasmiditan often had significant impairment of driving performance 90 minutes after taking it, and this problem driving continued for up to 8 hours after taking it. Driving or operating machinery for 8 hours after taking lasmiditan is not recommended.
- Summary of safety data – introduce table 2

Table 2: Adverse Reactions Related to Lasmiditan with a Frequency of 2% or Greater than Placebo

Adverse Reaction	Lasmiditan 50 mg	Lasmiditan 100 mg	Lasmiditan 200 mg	Placebo
Dizziness	9	15	17	3
Fatigue	4	5	6	1
Paresthesia	3	7	9	2
Sedation	6	6	7	2
Nausea/vomiting	3	4	4	2
Muscle weakness	1	1	2	0

- **Other warnings / precautions**:
    - Driving Impairment: Advise patients not to drive or operate machinery until at least 8 hours after taking each dose of lasmiditan. Patients who cannot follow this advice should not take lasmiditan. Patients may not be able to assess their own driving competence and the degree of impairment caused by lasmiditan.
    - CNS depression: May cause CNS depression, which may impair physical or mental abilities and cause significant driving impairment. Patients should not engage in activities requiring mental alertness, such as driving or operating heavy machinery, for at least 8 hours after administration. Patients may be unable to assess their own driving competence; patients unable to abstain from activities requiring mental alertness for at least 8 hours should not take lasmiditan.
    - Serotonin syndrome: Potentially life-threatening serotonin syndrome (SS) has occurred in patients receiving lasmiditan without any other drugs associated with SS. SS may also occur when used in combination with other serotonergic agents (e.g., selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, buspirone, St. John's wort, tryptophan) or agents that impair metabolism of serotonin (e.g., monoamine oxidase inhibitors [MAOIs] intended to treat psychiatric disorders, other MAOIs [i.e., linezolid and IV methylene blue]). Monitor patients closely for signs of SS, such as mental status changes (e.g., agitation, hallucinations, delirium, coma), autonomic instability (e.g., tachycardia, labile BP, diaphoresis), neuromuscular changes (e.g., tremor, rigidity, myoclonus), GI symptoms (e.g., nausea, vomiting, diarrhea), and/or seizures. Discontinue treatment (and any concomitant serotonergic agent) immediately if signs/symptoms arise.
    - Cardiovascular disease: Lasmiditan may decrease heart rate and/or increase BP; monitor closely in patients who may not tolerate these effects.
    - Hepatic impairment: Use is not recommended in patients with severe hepatic impairment.
    - Elderly: Dizziness and increases in systolic BP may occur more frequently in older adults.
    - Lasmiditan should not be taken with alcohol or other sedating medications. It is a controlled sub-stance, meaning that its use is monitored by the Drug Enforcement Agency (DEA).
- **Adverse reactions**
    - The most common TEAEs in the pooled Phase 3 controlled trials (at least 2% and at least 2% greater than placebo) were related to dizziness and balance disorder (up to 18%), somnolence, fatigue and sedation (up to 11%), asthenia, fatigue, malaise, and weakness (up to 8%), paresthesia and hypoesthesia (up to 8%), and nausea and vomiting (up to 4%). Overall, the database does not suggest cardiovascular or vascular risk. There was no imbalance in SAEs and AEs leading to discontinuation between lasmiditan vs placebo in placebo-controlled trials.

Other Therapeutic Options

Alternative treatments used as abortive headache therapies are listed in table 3 below

All triptans are limited to 18 doses per month. All triptans have level A evidence per the American Headache Society (2015) and American Family Physician (2018) Guidance.

Drug	Formulary status
Ubrogepant	NF
Rimegepant	NF
Almotriptan PO	NF
Eletriptan PO	F
Frovatriptan PO	NF
Naratriptan PO	NF
Rizatriptan PO	F
Rizatriptan ODT	F
Sumatriptan SubQ	F
Sumatriptan Nasal	F
Sumatriptan PO	F
Zolmitriptan ODT	F
Zolmitriptan PO	F
Zolmitriptan Nasal	F

Projected Place in Therapy

- Lasmiditan is a serotonin receptor agonist with high affinity to the 5-hydroxytryptamine 1F receptor.
- The intended use of lasmiditan is for the acute treatment of headache.
- Two phase III randomized, placebo-controlled trials evaluated the safety and efficacy of lasmiditan in comparison to placebo as an abortive therapy in headache. Patients treated a single headache episode in these trials. The efficacy results of these trials demonstrated a benefit of lasmiditan for this indication. Both studies used the same primary and key secondary endpoints (pain freedom at 2 hours and most bothersome symptom (photophobia, phonophobia, or nausea) freedom at 2 hours, respectively).
- Efficacy on pain freedom and MBS freedom at 2 hours was demonstrated at doses of 50 mg, 100 mg and 200 mg. The therapeutic gain (the percentage effect of active drug minus percentage effect of placebo) for pain freedom at 2 hours of lasmiditan compared to placebo, ranges from 7% for the 50 mg dose, to 10-13% for the 100 mg dose, and ~18% for the 200 mg dose. There is a dose-response seen for the primary endpoint of pain freedom at 2 hours.
- The safety and tolerability profile of lasmiditan reveals a high incidence of adverse CNS related events, such as dizziness, fatigue, vertigo, somnolence, and paresthesia. AEs rate increased when increasing lasmiditan dose. Additionally, patients should avoid activities that require mental alertness (such as driving) for at least 8 hours after taking the dose.
- Lasmiditan has been associated with euphoria and hallucinations. It is a controlled substance under the US Drug Enforcement Administration.
- For pain freedom or pain relief at 2 hours after the dose, lasmiditan, rimegepant, and ubrogepant were associated with higher odds ratios compared with placebo but lower odds ratios compared with most triptans[7]
- Lasmiditan's role will be primarily in the abortive treatment of acute migraine in patients that have a CV risk factor or disease for which triptan use is contraindicated.

References

[1] Center for Drug Evaluation and Research (CDER). Medical review of Lasmiditan (Reyvow). Food and Drug Administration (FDA). March 2019
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[4] Kuca B, Silberstein SD, Wietecha L, et al. Lasmiditan is an effective acute treatment for migraine: A phase 3 randomized study. Neurology. 2018;91(24):e2222-e2232.
[5] Brandes J, Kudrow D, Klise S, et al. Long-term Safety and Efficacy of Lasmiditan for Acute Treatment of Migraine Over a One-Year Period: Interim Results of an Open-Label Phase 3 Study (GLADIATOR) (P1.10-021). Neurology. 2019;92(15 Supplement):P1.10-021.
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