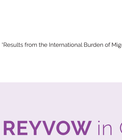
REYVOW™ (lasmiditan) CV tablets 50mg,100mg

The first and only ditan, a 5-HT$_{1F}$ receptor agonist, a new FDA-approved class for the acute treatment of migraine with or without aura in adults.
REYVOW is not indicated for the preventive treatment of migraine.

Patient Unmet Needs



A migraine attack can be painful and incapacitating.[1-3]

79% of patients said they experienced severe pain during a migraine attack.*[1]

Triptans are recommended as an acute therapy for migraine for appropriate patients by the American Headache Society.[4] However, **79% of patients** in a survey of 183 patients from 3 headache centers said they are willing to try another acute treatment.[5]

87% of people with migraine surveyed reported complete pain freedom provided by acute treatment is important or very important.[6]

*Results from the International Burden of Migraine Study (IBMS), a web-based survey of 9715 adults with migraine from 10 countries, of whom 57.1% had chronic migraine.

REYVOW in Clinical Studies

2 Clinical Trials

Randomized, double-blind placebo-controlled, single-attack trials.[7]

4439 Patients

who were 18 and older, with a history of migraine with or without aura according to the International Classification of Headache Disorders (ICHD-II) diagnostic criteria, who took a dose of REYVOW (3177) or placebo (1262).[7]

3 Doses

50mg[‡] **100mg** **200mg** (100mg x 2)

[‡]*50mg dose only in one study*

Efficacy Endpoints:

Pain Freedom
The efficacy of REYVOW was demonstrated by its ability to provide patients with complete elimination of moderate to severe headache pain at 2 hours.[7]

Across 2 studies and 3 doses, 28-39% of patients **achieved complete elimination of migraine pain at 2 hours** with REYVOW vs. 15-21% with placebo.[7]

- **SPARTAN 50 mg:** n=544; Difference from placebo=7%; *P*=0.014
- **SAMURAI and SPARTAN 100 mg:** n=1021; Differences from placebo=13% and 10%; *P*<0.001
- **SAMURAI and SPARTAN 200 mg**: n=1024; Differences from placebo=17% and 18%; *P*<0.001
- **SAMURAI and SPARTAN Placebo:** n=1049

Patients were instructed to take the study drug within 4 hours of headache onset and when the pain was moderate to severe.[7]

Freedom From MBS
The efficacy of REYVOW was demonstrated by its ability to provide patients with complete elimination of most bothersome symptom (MBS: patient-selected from sensitivity to light, sensitivity to sound, or nausea) at 2 hours.[7]

Across 2 studies and 3 doses, 41-49% of patients **achieved freedom from their MBS at 2 hours** with REYVOW vs. 30-33% with placebo.[7]

- **SPARTAN 50 mg:** n=502; Difference from placebo=8%; *P*=0.014
- **SAMURAI and SPARTAN 100 mg:** n=955; Differences from placebo=12% and 11%; *P*<0.001
- **SAMURAI and SPARTAN 200 mg**: n=945; Differences from placebo=11% and 16%; *P*<0.001
- **SAMURAI and SPARTAN Placebo:** n=989

Patients were allowed to take a rescue medication 2 hours after taking study drug; however, opioids, barbiturates, triptans, and ergots were not allowed within 24 hours of study drug administration.[7]

Select Important Safety Information - Driving Impairment

REYVOW may cause significant driving impairment. More sleepiness was reported at 8 hours compared to placebo. Advise patients not to engage in potentially hazardous activities requiring complete mental alertness, such as driving a motor vehicle or operating machinery, for at least 8 hours after each dose of **REYVOW.** Patients who cannot follow this advice should not take **REYVOW.** Prescribers and patients should be aware that patients may not be able to assess their own driving competence and the degree of impairment caused by **REYVOW.**[7]

The warnings and precautions for REYVOW are driving impairment, central nervous system (CNS) depression, serotonin syndrome, and medication overuse headache.[7] See Important Safety Information below.

Most common adverse reactions occurring in greater than or equal to 2% and at a frequency greater than placebo.[7]

	REYVOW 200mg (n=1258)	REYVOW 100mg (n=1265)	REYVOW 50mg (n=654)	Placebo (n=1262)
Dizziness*	17%	15%	9%	3%
Fatigue[A]	6%	5%	4%	1%
Paresthesia[B] (a tingling or numbing sensation on the skin)	9%	7%	3%	2%
Sedation[C] (sleepiness or drowsiness)	7%	6%	6%	2%
Nausea and/or vomiting	4%	4%	3%	2%
Muscle weakness	2%	1%	1%	0%

[A] Fatigue includes the adverse reaction related terms asthenia and malaise.
[B] Paresthesia includes the adverse reaction related terms paresthesia oral, hypoesthesia, and hypoesthesia oral.
[C] Sedation includes the adverse reaction related term somnolence.
*In general, dizziness was mild or moderate in severity.[8]

REYVOW is a non-opioid/non-narcotic, Schedule V controlled substance due to its low abuse potential and no evidence of physical dependence. The Drug Enforcement Administration (DEA) schedules drugs from I to V, with I being the highest potential for abuse and/or dependence and V being the lowest potential for its abuse and/or dependence. See additional information about REYVOW abuse potential in the Important Safety Information below.

REYVOW Mechanism of Action

REYVOW is a high-affinity 5-HT$_{1F}$ receptor agonist (ditan) that presumably exerts its therapeutic effects by binding to and activating this receptor. However, the exact mechanism of action is unknown.[7]

SEROTONIN (5-HT) 1F RECEPTORS MAY PLAY A ROLE IN MIGRAINE[9,10]

Activation of 5-HT$_{1F}$ receptors has been observed in preclinical studies to[9,11-13]:

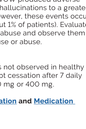
Inhibit pain pathways, including the nerve responsible for sensation in the face and motor functions (trigeminal nerve).

Inhibit the release of neurotransmitters and neuropeptides that may play a role in migraine.

Not cause vasoconstriction of blood vessels.

COMMITMENT TO PATIENTS

Lilly is committed to redefining treatment expectations for this debilitating neurologic disease. Complete elimination of pain should be the primary goal of acute treatment for migraine, and REYVOW can offer patients the chance for fast and complete elimination of moderate to severe migraine pain and their most bothersome symptom at 2 hours.



For more information about REYVOW, visit **www.REYVOW.com**. To learn about the REYVOW Savings Card Program, visit **www.REYVOW.com/Savings**. Governmental beneficiaries excluded, subject to terms and conditions.

IMPORTANT SAFETY INFORMATION FOR REYVOW

WARNINGS AND PRECAUTIONS

Driving Impairment
REYVOW may cause significant driving impairment. In driving studies, administration of single 50 mg, 100 mg, or 200 mg doses of REYVOW significantly impaired subjects' ability to drive. Additionally, more sleepiness was reported at 8 hours compared to placebo. Advise patients not to engage in potentially hazardous activities requiring complete mental alertness, such as driving a motor vehicle or operating machinery, for at least 8 hours after each dose of REYVOW. Patients who cannot follow this advice should not take REYVOW. Prescribers and patients should be aware that patients may not be able to assess their own driving competence and the degree of impairment caused by REYVOW.

Central Nervous System Depression
REYVOW may cause central nervous system (CNS) depression, including dizziness and sedation. Because of the potential for REYVOW to cause sedation, other cognitive and/or neuropsychiatric adverse reactions, and driving impairment, REYVOW should be used with caution if used in combination with alcohol or other CNS depressants. Patients should be warned against driving and other activities requiring complete mental alertness for at least 8 hours after REYVOW is taken.

Serotonin Syndrome
In clinical trials, reactions consistent with serotonin syndrome were reported in patients treated with REYVOW who were not taking any other drugs associated with serotonin syndrome. Serotonin syndrome may also occur with REYVOW during coadministration with serotonergic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase (MAO) inhibitors). Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular signs (e.g., hyperreflexia, incoordination), and/or gastrointestinal signs and symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication. Discontinue REYVOW if serotonin syndrome is suspected.

Medication Overuse Headache
Overuse of acute migraine drugs (e.g., ergotamines, triptans, opioids, or a combination of drugs for 10 or more days per month) may lead to exacerbation of headache (i.e., medication overuse headache). Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients including withdrawal of the overused drugs and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

ADVERSE REACTIONS

The most common adverse reactions associated with REYVOW (≥2% and greater than placebo in clinical studies) were dizziness, fatigue, paresthesia, sedation, nausea and/or vomiting, and muscle weakness.

DRUG ABUSE AND DEPENDENCE

REYVOW contains lasmiditan, a Schedule V controlled substance.

Abuse
In a human abuse potential study in recreational poly-drug users (n=58), single oral therapeutic doses (100 mg and 200 mg) and a supratherapeutic dose (400 mg) of REYVOW were compared to alprazolam (2 mg) (C-IV) and placebo. With all doses of REYVOW, subjects reported statistically significantly higher "drug liking" scores than placebo, indicating that REYVOW has abuse potential. Subjects who received REYVOW reported statistically significantly lower "drug liking" scores than alprazolam. Euphoric mood occurred to a similar extent with REYVOW 200 mg, REYVOW 400 mg, and alprazolam 2 mg (43-49%). A feeling of relaxation was noted in more subjects on alprazolam (22.6%) than with any dose of REYVOW (7-11%). Phase 2 and 3 studies indicate that, at therapeutic doses, REYVOW produced adverse events of euphoria and hallucinations to a greater extent than placebo. However, these events occur at a low frequency (about 1% of patients). Evaluate patients for risk of drug abuse and observe them for signs of lasmiditan misuse or abuse.

Dependence
Physical withdrawal was not observed in healthy subjects following abrupt cessation after 7 daily doses of lasmiditan 200 mg or 400 mg.

See Prescribing Information and Medication Guide.

LM HCP ISI 11JAN2020

References:
[1]Rayne KA, Varon SF, Kawata AK, et al. The International Burden of Migraine Study (IBMS): Study design, methodology, and baseline cohort characteristics. *Cephalalgia*. 2011;31:1116-1130. [2]Stewart WF, Lipton RB. The economic and social impact of migraine. *Eur Neurol*. 1994;34(suppl 2):12-17. [3]Brandes J. Global trends in migraine care: results from the MAZE survey. *CNS Drugs*. 2002;16(suppl 1):13-18. [4]American Headache Society. The American Headache Society Position Statement on Integrating New Migraine Treatments Into Clinical Practice. *Headache*. 2019;59:1-18. [5]Bigal M, Rapoport A, Aurora S, et al. Satisfaction with current migraine therapy: experience from 3 centers in US and Sweden. *Headache*. 2007;47:475-479. [6]Lipton RB, Stewart WF. Acute migraine therapy: do doctors understand what patients with migraine want from therapy? *Headache*. 1999;39(suppl 2):S20-S26. [7]REYVOW (Prescribing Information). Indianapolis, IN: Lilly USA, LLC. [8]Krege JH, Rizzoli PB, Litflick E, et al. Safety findings from Phase 3 lasmiditan studies for acute treatment of migraine: Results from SAMURAI and SPARTAN. *Cephalalgia*. 2019;39:957-968. [9]Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffman J, et al. Pathophysiology of a migraine: a disorder of sensory processing. *Physiol Rev*. 2017;97:553-622. [10]Ramadan N, Saljuqevski V, Phebus, L., Johnson K. 5-HT$_{1F}$ receptor agonists in acute migraine treatment: a hypothesis. *Cephalalgia*. 2003;23:776-785. [11] Ahn SK, Khalmuratova R, Jeon SY, et al. Colocalization of 5-HT1F receptor and calcitonin gene-related peptide in rat vestibular nuclei. *Neuroscience Letters*. 2009;465:151-156. [12]Rubio-Beltran E, Labastida-Ramirez A, Villalon CM, MaassenVanDenBrink A. Is selective 5-HT1F receptor agonism an entity apart from that of the triptans in antimigraine therapy? *Pharmacol Ther*. 2018;186:88-97. [13]Arulmani U, VanDenBrink AM, Villalon CM, Saxena PR. Calcitonin gene-related peptide and its role in migraine pathophysiology. *Eur J Pharmacol*. 2004;500:315-330.