

Lasmiditan

Brand Name: Reyvow

Generic Name: lasmiditan

Manufacturer^{1,4}: Eli Lilly

Drug Class^{1,2,3,4}: Serotonin 5-HT_{1F} Receptor Agonist

Uses:

Labeled^{1,2,3,4}: acute treatment of migraine

Unlabeled: none

Mechanism of Action^{1,2,3,4}:

Lasmiditan has high affinity to 5-HT_{1F} receptor, but the full mechanism of action is unknown. It may decrease stimulation of the trigeminal system within meninges. 5-HT_{1B} receptors in blood vessels are not activated, so vasoconstriction does not occur.

Pharmacokinetics^{1,2,3,4}:

Tmax	1.8 hrs
Vd	Not reported
t _{1/2}	5.7 hours
Clearance	Not reported
Protein binding	55-60%
Bioavailability	Not reported

Metabolism: lasmiditan undergoes hepatic and extrahepatic metabolism primarily by ketone reduction. None of the following enzymes are involved in the metabolism; MAO-A, MAO-B, flavin monooxygenase 3, CYP450 reductase, xanthine oxidase, alcohol dehydrogenase, aldehyde dehydrogenase, and aldo-keto reductases. Metabolized into M7 and M18 both of which are inactive.

Elimination: Renal excretion is a minor route of elimination with only 3% of unchanged drug being excreted in the urine.

Efficacy:

Färkkilä M, Diener HC, Géraud G, et al. Efficacy and tolerability of lasmiditan, an oral 5-HT_{1F} receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study. *Lancet Neurol.* 2012;11(5):405-413. doi:10.1016/S1474-4422(12)70047-9

Study design: multisite, double-blind, randomized, parallel, placebo-controlled trial

Description of study: *Methods:* five-hundred-twelve participants were enrolled to receive lasmiditan 50mg, 100mg, 200mg, 400mg, or placebo. Participants took a single dose of the medication to treat a moderate to severe migraine attack. Baseline and post-dose severity ratings were reported in a standardized paper diary. The primary outcome measure was percentage of participants with headache response two hours post-dose. Safety/tolerability were evaluated by assessing treatment emergent adverse events that occurred during the study. *Outcome results:* The percentage of participants who achieved headache response at two hours was significantly higher for those taking 400mg (65% [95%CI 52.2-75.9], p<0.0001), 200mg (51% [95%CI 38.4-63.0], p=0.0018), 100mg (64% [95%CI 52.8-74.6], p<0.0001), and 50mg (43% [95%CI 31.9-54.7], p=0.022) compared to placebo (25.9% [95%CI 16.8-36.9]). The percentage of participants that achieved pain freedom at two hours was significant for the 200mg (28%, p=0.007) and 400mg (19%, p=0.032) groups compared to placebo (7.4%). Adverse events were reported in 20% of the 50mg group, 28% of the 100mg group, 39% of the 200mg group, and 44% of the 400mg group compared to 6% of the placebo group. A majority of the adverse events seen were mild to moderate, and the most common severe adverse event recorded in all groups was dizziness.

Limitations: All authors of the study are affiliated with CoLucid Pharmaceuticals (Eli Lilly) who sponsored/funded the study. The study sponsor was involved in data collection, analyses, and interpretation. Patients with contraindications to triptans were excluded from the study. Only a single dose of medication was studied, and there is a need to look at longer term effects with longer duration studies. The study had a small sample size.

Conclusion: The study showed all four doses of lasmiditan produced a significant headache response two hours after the dose but only the higher doses had a significant proportion of patients achieve pain freedom at two hours. This supports the use of lasmiditan for acute treatment of migraine. However, generalization of the results may be limited by exclusion criteria and the relatively small sample size, therefore, larger scale studies will need to be conducted.

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. doi:10.1212/WNL.0000000000006641a

Study design: randomized, double-blind, parallel, placebo-controlled trial

Description of study: *Methods:* 2231 participants were randomized to receive lasmiditan 200mg, lasmiditan 100mg, or placebo. A total of 1865 received treatment and were included in the safety population. A dose of medication was taken within four hours of migraine onset with moderate to severe pain. A second dose of medication was optionally taken 2-24hours after the first dose, participants in the treatment groups were randomized

2:1 to receive a second dose of lasmiditan or placebo. Efficacy was evaluated using an electronic diary where baseline migraine severity and most bothersome symptom were recorded. Safety and tolerability were also assessed at a follow-up visit. *Outcome results:* Percentage of participants free of migraine pain two hours after dose that received lasmiditan 200mg (32.2%, OR 2.6 [95%CI 2.0-3.6], $p<0.001$) and lasmiditan 100mg (28.2%, OR 2.2[95%CI 1.6-3.0] $p<0.001$) was significantly higher compared to placebo (15.3%). Percentage of participants that were free of their most bothersome symptom (photophobia, phonophobia, nausea) two hours after the dose was significantly higher in the 200mg group (40.7%, $p<0.001$) and 100mg group (40.9%, $p<0.001$) compared to placebo (29.5%). Sustained pain freedom at twenty-four hours after dose was significantly higher for participants who took lasmiditan 200mg (18.6%, $p<0.001$) and lasmiditan 100mg (14.8%, $p<0.001$) compared to placebo (7.6%). The percentage of participants that experienced pain relief two hours after dose was significantly higher for lasmiditan 200mg group (59.5%, $p<0.001$) and lasmiditan 100mg group (59.4%, $p<0.001$) compared to the placebo group (42.2%). 42.7% of the lasmiditan 200mg group, 36.3% of the lasmiditan 100mg group, 16.4% of the placebo group experienced at least one treatment emergent adverse event after the first dose of medication. Dizziness was the most common adverse event seen for all three groups. The incidence of cardiovascular adverse events after the first dose was low; with palpitations seen in 3 participants (0.5%) in the lasmiditan 200mg group and 2 participants (0.3%) in the lasmiditan 100mg group.

Limitations: All authors were employees, stockholders, or consultants to CoLucid Pharmaceuticals, Inc (Eli Lilly), the manufacturer of lasmiditan. Participants took medication at home and self-reported data in an electronic diary without monitoring from study facilitators. Lack of adherence to recording in diary may have decreased the quality of data collected.

Conclusion: Lasmiditan showed significantly higher percentage of pain freedom after two hours compared to placebo for both dosages. The percentage of participant who experienced absence of most bothersome symptom was significantly higher for both doses of lasmiditan compared to placebo. Treatment with lasmiditan was relatively well tolerated with the most common adverse event seen being dizziness. Lasmiditan may be a potential option for patients who have failed therapy or have contraindications to current migraine treatments.

Goadsby PJ, Wietecha LA, Dennehy EB, et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. *Brain*. 2019;142(7):1894-1904. doi:10.1093/brain/awz134

Study design: prospective, randomized, double-blind, placebo-controlled, multisite trial

Description of study: *methods:* Participants (n=2869) were randomized 1:1:1:1 to receive lasmiditan 200mg, 100mg, 50mg, or placebo, which they took within four hours of migraine onset, if pain was moderate to severe and not improving. An optional second dose of the medication could be taken two to twenty-four hours after the first dose if headache was not improving. Post-dose headache severity and presence of most bothersome symptom were recorded for 48 hours after first dose. Safety and tolerability were assessed in all participants that took at least one dose of the medication. *Outcome results:* The percentage of participants who were pain free at two hours was significantly

higher in the lasmiditan 200mg group (38.8%, OR 2.3 [95%CI 1.8-3.1], $p<0.001$) compared to placebo (21.3%). Lasmiditan 100mg (31.4%, OR 1.7 [95% CI 1.3-2.2] $p<0.001$) and 50mg (28.6%, OR 1.5 [95%CI 1.1-1.9], $p=0.003$) groups also had significantly higher percentages of pain freedom two hours after the dose compared to placebo (21.3%). The percentage of participants that were free of the most bothersome symptom two hours after the dose was significantly higher for 200mg (48.7%, $p<0.001$), 100mg (44.2%, $p<0.001$), and 50mg (40.8%, $p=0.009$) groups compared to placebo (33.5%). Sustained pain freedom at twenty-four hours was significantly higher for participants who took lasmiditan 200g (22.7%, $p<0.001$), 100mg (17.9%, $p=0.021$), and 50mg (17.2%, $p=0.036$) compared to placebo (13.4%). 39% of participants in the 200mg group, 36.1% of the 100mg group, 25.4% in the 50mg group, and 11.6% in the placebo group experienced at least one treatment emergent adverse event during the study. The most reported adverse event in all four groups was dizziness. Cardiovascular adverse effects were rare, with palpitations occurring in two participants (0.3%) in each treatment group.

Limitations: All authors have ties with Eli Lilly/CoLucid Pharmaceuticals who funded the study. Eli Lilly/CoLucid Pharmaceuticals participated in data collection, analyses, and interpretation. A majority of participants enrolled in the study were middle-aged white females, limiting extrapolated to other patient populations. Only a small number of participants enrolled had cardiovascular disease and more studies are needed in this patient population to determine safety and efficacy. The study only assessed a single attack, longer duration studies are needed to evaluate long term safety and efficacy of lasmiditan.

Conclusion: The study showed all three strengths of lasmiditan significantly improved the rates of pain freedom, and absence of most bothersome symptoms two hours after a dose compared to placebo. Lasmiditan was well tolerated with no serious adverse events reported during the study. This supports the use of lasmiditan as a treatment of acute migraine attacks. Studies need to be conducted that include more patients with cardiovascular disease, to evaluate the efficacy and safety in this patient population. Longer duration studies also need to be conducted to get an idea of long-term safety and efficacy of lasmiditan when used for more than one migraine attack.

Contraindications^{1,2,3}:

None reported

Precautions^{1,2,3,4}:

Driving impairment: lasmiditan can significantly impair patient's ability to drive. Patients should be advised to not engage in potentially dangerous activities that require mental awareness for at least eight hours after taking lasmiditan, and that they may not be able to gauge the degree of their own impairment.

Central Nervous system depression: lasmiditan may cause CNS depression including dizziness and sedation, other cognitive adverse reactions are possible. Due to possible CNS depressive effects patient should use caution if used in combination with alcohol or other CNS depressants.

Serotonin syndrome: serotonin syndrome may occur when lasmiditan is used in combination with serotonergic drugs (i.e. SSRIs, SNRIs, TCAs). Reactions consistent to

serotonin syndrome were seen in patients receiving lasmiditan but not a serotonergic agent. Signs of serotonin syndrome include mental status changes, autonomic instability, neuromuscular symptom, or gastrointestinal distress. Onset of symptoms can occur minutes to hours after dose. Lasmiditan should be discontinued if serotonin syndrome is suspected.

Medication overuse headache: Overuse of acute migraine medications, use on ten or more days a month, may lead to exacerbation of headaches. Medication overuse headaches may present as migraine-headaches daily or increase in migraine attacks.

Cardiovascular disease: Lasmiditan may decrease heart rate or increase blood pressure. Patients with cardiovascular disease who may not be able to tolerate these changes should be closely monitored while using lasmiditan.

Adverse effects^{1, 2}:

Occurring in >10% of patients

Central Nervous system

dizziness (9-17%)

Occurring in 1-10% of population

Cardiovascular

Chest discomfort (<2%)

palpitations (<2%)

Central nervous system

Paresthesia (3% to 9%)

drowsiness (6% to 7%)

fatigue (4% to 6%)

abnormal dreams (<2%)

anxiety (<2%)

ataxia (<2%)

cognitive dysfunction (<2%)

confusion (<2%)

euphoria (<2%)

feeling abnormal (<2%)

hallucination (<2%)

lethargy (<2%)

local discomfort (limb: <2%)

restlessness (<2%)

sleep disturbance (<2%)

speech disturbance (<2%)

vertigo (<2%),

myasthenia (1% to 2%)

Gastrointestinal

Nausea (≤4%)

vomiting (≤4%)

Neuromuscular & skeletal

Muscle spasm (<2%)

tremor (<2%)

Ophthalmic

Visual impairment (<2%)

Respiratory

Dyspnea (<2%)

Occurring in <1% of patients

Angioedema

hypersensitivity reaction

skin photosensitivity

skin rash

Frequency not defined

Cardiovascular

Decreased heart rate

increased blood pressure

Central nervous system

Central nervous system depression

Drug Interactions^{1,2,3,4}:

Serotonergic agents

SSRIs, SNRIs, TCAs, MAOIs, amphetamines, dextromethorphan, bupropion, buspirone, amphetamines, triptans, 5HT₃ receptor antagonists, dopaminergic agents, St. john's wort. Concomitant use increases the risk of serotonin syndrome.

CNS depressants

Muscle relaxers, barbiturates, benzodiazepines, opioids, sedating H-1 blockers, antipsychotics, TCAs, cannabidiol, hypnotics, alcohol (ethanol), gabapentin. Concomitant use has not been evaluated, but due to the potential of sedation and other cognitive effects the use of lasmiditan with CNS depressants should be avoided.

Heart rate lowering agents

Beta blockers, calcium-channel blockers, ceritinib, digoxin. Concomitant use could increase bradycardia.

BCRP substrates

Lasmiditan inhibited BCRP in vitro. Concomitant use with substrates should be avoided.

P-GP substrates

Statins, digoxin. Lasmiditan inhibited P-gp in vitro. Concomitant use with substrates should be avoided.

Dosing/ Administration^{1,2,3}:

Usual dose: 50mg, 100mg, or 200mg single dose as needed for migraine. Max 1 dose per 24 hours

Geriatric dose: initiate at low end of dosing range.

Hepatic impairment dose:

mild (Child-Pugh A) or moderate (Child-Pugh B): no dosage change needed

severe (Child-Pugh C): Use not recommended

Use in special circumstances^{1,2,3,4}:

Pregnancy: There is no adequate data on safety in humans, but developmental adverse events were seen in animal reproduction studies.

Lactation: It is unknown if lasmiditan is present in breast milk. Benefits and risks need to be looked before mothers breastfeed while taking lasmiditan.

Pediatric Use: Safety and efficacy of lasmiditan has not been studied in children.

Geriatric Use: Dizziness and increased systolic blood pressure may occur more frequently in patients over sixty-five years old.

Hepatic Impairment: The use of lasmiditan is not recommended in patients with severe hepatic impairment, use has not been studied.

Conclusion: Lasmiditan potentially has a place in therapy for the treatment of acute migraines as an alternative to patients who have contraindications to or have not responded to current treatment options. Since lasmiditan does not cause vasoconstriction it may be a safe option for patients who have cardiovascular disease and other cardiovascular contraindications to triptans, but more studies are needed to evaluate the safety and efficacy of lasmiditan in these patients. The studies found that lasmiditan significantly increase the rate of pain freedom two hours after dose compared to placebo in clinical trials. These trials also found lasmiditan to be relatively well tolerated seeing low incidence of adverse events during the studies. However, more studies with longer durations need to be conducted to evaluate the long-term safety profile of lasmiditan before we know its true place in therapy.

Recommended references:

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- (2) Lasmiditan. Lexi-Drugs [online database]. LexiComp, 2020. Accessed June 01, 2020.
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- (4) Reyvow [package insert]. Indianapolis, IN. Lilly USA, LLC; 2019.
- (5) Färkkilä M, Diener HC, Géraud G, et al. Efficacy and tolerability of lasmiditan, an oral 5-HT_{1F} receptor agonist, for the acute treatment of migraine: a phase 2 randomised, placebo-controlled, parallel-group, dose-ranging study. *Lancet Neurol.* 2012;11(5):405-413. doi:10.1016/S1474-4422(12)70047-9
- (6) 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. doi:10.1212/WNL.0000000000006641a
- (7) Goadsby PJ, Wietecha LA, Dennehy EB, et al. Phase 3 randomized, placebo-controlled, double-blind study of lasmiditan for acute treatment of migraine. *Brain.* 2019;142(7):1894-1904. doi:10.1093/brain/awz134

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