Lilly's REYVOW™ (lasmiditan), The First and Only Medicine in a New Class of Acute Treatment for Migraine, Receives FDA Approval

- The approval of REYVOW is significant because it represents the first new class of acute migraine treatment approved by the FDA in more than two decades

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INDIANAPOLIS, Oct. 11, 2019 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) announced today that the U.S. Food and Drug Administration (FDA) has approved REYVOW™ (lasmiditan) an oral medication for the acute treatment of migraine, with or without aura, in adults. REYVOW has a unique mechanism of action and is the first and only FDA-approved medicine in a new class of acute treatment for migraine (serotonin (5-HT)1F receptor agonists).

"Millions of people with migraine face an ongoing battle with the unresolved pain and symptoms of a migraine attack. There is a substantial unmet need for new acute treatments for migraine, like REYVOW, which is why we are proud of today's approval and Lilly's continuing contribution to the migraine community," said Gudarz Davar, M.D., vice president, neurology development, Lilly Bio-Medicines. "New expectations have been set in migraine care; pain

freedom is now the treatment goal for people living with migraine and those who treat them. At Lilly, we are pioneering innovative medicines to provide new options for patients with migraine."

As with other medicines with central nervous system (CNS) activity, the FDA required abuse potential studies for REYVOW. Abuse potential refers to the likelihood that abuse will occur with a particular drug product or substance with CNS activity. Consistent with the FDA's guidance, Lilly conducted a human abuse potential assessment; as part of that assessment, therapeutic doses of REYVOW were associated with less drug liking when compared to alprazolam, but more than placebo. The recommended controlled substance classification for REYVOW is currently under review by the Drug Enforcement Administration (DEA) and is expected within 90 days of today's FDA approval, after which REYVOW will be available to patients in retail pharmacies.

"As a physician who specializes in the treatment of migraine and headache disorders, I commonly treat patients who are looking for acute treatment options that offer the chance for pain freedom during migraine attacks. This approval is especially significant because migraine pain is so often severe and incapacitating," said Jan Brandes, M.D., MS, FAAN, assistant clinical professor, Department of Neurology, Vanderbilt University. "With new science comes new hope. Considering up to 40% of people with migraine do not get adequate responses from their initial acute treatment prescription, having a new and novel option like REYVOW is an important development for physicians and the patients we treat.[1,2,3,4]"

The New Drug Application (NDA) for REYVOW included data from two Phase 3 single-attack studies (SAMURAI and SPARTAN), which evaluated the safety and efficacy of REYVOW for the acute treatment of migraine in adults. Both studies met the efficacy endpoints of pain freedom and freedom from most bothersome symptom (MBS; patient selected from nausea, sensitivity to light, or sensitivity to sound) at two hours following administration of REYVOW in comparison to placebo. Treatment emergent adverse events were generally mild to moderate and the most frequent included dizziness, fatigue, paresthesia (tingling or numbing sensation on the skin), sedation (sleepiness or drowsiness), nausea and/or vomiting and muscle weakness. See additional Important Safety Information below.

The REYVOW Phase 3 development program, including the open-label GLADIATOR study, involved more than 4,000 patients and the treatment of more than 20,000 migraine attacks.

"For over 25 years, Lilly has been committed to helping people affected by disabling headache disorders, investigating more than a dozen different compounds," said Patrik Jonsson, senior vice president and president, Lilly Bio-Medicines. "The approval of REYVOW is an exciting development for patients and physicians seeking the potential for pain freedom when a migraine attack happens."

About REYVOW™ (lasmiditan)

REYVOW is a new oral treatment that binds to 5-HT_{1F} receptors with high affinity and is approved by the FDA for the acute treatment of migraine, with or without aura, in adults. Its therapeutic effects are presumably mediated by agonist effects at this receptor; however, the precise mechanism is unknown. REYVOW is not indicated for preventive treatment of migraine. Once available, REYVOW can be prescribed to patients in oral doses of 50 mg, 100 mg, and 200 mg as needed.

IMPORTANT SAFETY INFORMATION FOR REYVOW

Warnings and Precautions

Driving Impairment

REYVOW may cause significant driving impairment. In a driving study, 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 (Controlled substance schedule to be determined after review by the Drug Enforcement Administration.)

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.

Full Prescribing Information and Medication Guide.

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About Migraine

Migraine is a neurologic disease characterized by recurrent episodes of severe headache accompanied by other symptoms including nausea, sensitivity to light and sensitivity to sound.[5,6] More than 30 million American adults have migraine, with three times more women affected by migraine compared to men.[7] According to the Medical Expenditures Panel Survey, total annual healthcare costs associated with migraine are estimated to be as high as $56 billion annually in the United States, yet it remains under-recognized and under-treated.[8]

About Lilly's Commitment to Headache Disorders

For over 25 years, Lilly has been committed to helping people affected by headache disorders, investigating more than a dozen different compounds for the treatment of migraine and cluster headache. These research programs have accelerated our understanding of these diseases and furthered the advancement of treatments for headache disorders including REYVOW, approved by the FDA for the acute treatment of migraine, with or without aura, in adults. Our goal is to apply our combined clinical, academic and professional experience to build a research portfolio that delivers comprehensive solutions and addresses the needs of people affected by these disabling neurologic diseases.

About Eli Lilly and Company

Lilly is a global health care leader that unites caring with discovery to create medicines that make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at lilly.com and lilly.com/newsroom. P-LLY

This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about REYVOW (lasmiditan) as an acute treatment for patients with migraine and reflects Lilly's current belief. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. These forward-looking statements are based on the company's current plans, objectives, estimates, expectations and intentions and inherently involve significant risks and uncertainties. Commercialization and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and

uncertainties, which include, without limitation, risks and uncertainties associated with: the company's ability to effectively commercialize REYVOW in the U.S.; delays or problems in the supply or manufacture of REYVOW; obtaining and maintaining appropriate pricing and reimbursement for REYVOW; complying with applicable U.S. regulatory requirements; any delays in, or the outcome of, scheduling by the U.S. Drug Enforcement Administration (DEA) for REYVOW; and other risks and uncertainties affecting the company. For further discussion of these and other risks and uncertainties, see Lilly's most recent Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

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Refer to: Jen Dial; dial_jennifer_kay@lilly.com; 317-220-1172 (Lilly Bio-Medicines)
Kevin Hern; hern_kevin_r@lilly.com; 317-277-1838 (Investor Relations)

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