HARMONY BIOSCIENCES HIGHLIGHTS PUBLICATION OF NARCOLEPSY TREATMENT SCIENTIFIC REVIEW IN SLEEP MEDICINE

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Article reviews mechanisms of action (MOA) of medications used in the treatment of patients with narcolepsy and clinical implications

PLYMOUTH MEETING, PA, March 30, 2020 —Harmony Biosciences, LLC ("Harmony"), a private pharmaceutical company dedicated to developing and commercializing novel treatment options for people living with rare diseases, announced today that *Sleep Medicine* has published an article which reviews the mechanism of action (MOA) of available treatments for patients with narcolepsy.

The article, "Update on the Pharmacologic Management of Narcolepsy: Mechanisms of Action and Clinical Implications," authored by Dr. Michael J. Thorpy and Dr. Richard K. Bogan was published online in September 2019 and will appear in print in the April 2020 issue of the journal. As patients with narcolepsy require ongoing pharmacologic management to reduce symptoms and improve functioning, the goal of the article is to review the multiple neurotransmitter systems that are important to maintaining wakefulness and analyze various treatment options along with their MOAs for patients living with narcolepsy. Further, the article discusses clinical implications of differences in MOA between treatments. Among those discussed is WAKIX®(pitolisant) and its differentiated MOA that increases histamine transmission in the brain and the release of other neurotransmitters that promote wakefulness.

"Harmony is committed to furthering research for the treatment of patients with narcolepsy with the aim to help those living with this rare disorder," said Harmony's Chief Medical Officer, Jeffrey Dayno, M.D. "This publication provides healthcare professionals an important resource to inform key considerations such as mechanism of action, pharmacokinetics and abuse potential when evaluating potential treatment options for patients with narcolepsy."

About WAKIX (pitolisant) tablets
WAKIX is a first-in-class medication approved by the U.S. Food and Drug Administration in August 2019 for the treatment of excessive daytime sleepiness in adult patients with narcolepsy. It was granted orphan drug designation for the treatment of narcolepsy in 2010. WAKIX is a selective histamine 3 (H_3) receptor antagonist/inverse agonist. The mechanism of action of WAKIX is unclear; however, its efficacy could be mediated through its activity at H_3 receptors, thereby increasing the synthesis and release of histamine, a wake promoting neurotransmitter. WAKIX was designed and developed by Bioprojet Societe Civile de Recherche (Bioprojet), who has marketed the product in Europe since its approval by the European Medicines Agency in 2016. Harmony has an exclusive license from Bioprojet to develop, manufacture and commercialize pitolisant in the United States.

INDICATIONS AND USAGE
WAKIX is indicated for the treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy.

IMPORTANT SAFETY INFORMATION

Contraindications
WAKIX is contraindicated in patients with severe hepatic impairment.

Warnings and Precautions
WAKIX prolongs the QT interval; avoid use of WAKIX in patients with known QT prolongation or in combination with other drugs known to prolong the QT interval. Avoid use in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval.

The risk of QT prolongation may be greater in patients with hepatic or renal impairment due to higher concentrations of pitolisant; monitor these patients for increased QTc. Dosage modification is recommended in patients with moderate hepatic impairment and moderate or severe renal impairment (see full prescribing information). WAKIX is not recommended in patients with end-stage renal disease (ESRD).

Adverse Reactions
In the placebo-controlled clinical trials conducted in patients with narcolepsy with or without cataplexy, the most common adverse reactions (≥5% and twice placebo) for WAKIX were insomnia (6%), nausea (6%), and anxiety (5%). Other adverse reactions that occurred at ≥2% and more frequently than in patients treated with placebo included headache, upper respiratory infection,

musculoskeletal pain, heart rate increased, hallucinations, irritability, abdominal pain, sleep disturbance, decreased appetite, cataplexy, dry mouth, and rash.

Drug Interactions
Concomitant administration of WAKIX with strong CYP2D6 inhibitors increases pitolisant exposure by 2.2-fold. Reduce the dose of WAKIX by half.

Concomitant use of WAKIX with strong CYP3A4 inducers decreases exposure of pitolisant by 50%. Dosage adjustments may be required (see full prescribing information).

H1 receptor antagonists that cross the blood-brain barrier may reduce the effectiveness of WAKIX. Patients should avoid centrally acting H1 receptor antagonists.

WAKIX is a borderline/weak inducer of CYP3A4. Therefore, reduced effectiveness of sensitive CYP3A4 substrates may occur when used concomitantly with WAKIX. The effectiveness of hormonal contraceptives may be reduced when used with WAKIX and effectiveness may be reduced for 21 days after discontinuation of therapy.

Use in Specific Populations
WAKIX may reduce the effectiveness of hormonal contraceptives. Patients using hormonal contraception should be advised to use an alternative non-hormonal contraceptive method during treatment with WAKIX and for at least 21 days after discontinuing treatment.

There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to WAKIX during pregnancy. Patients should be encouraged to enroll in the WAKIX pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call 1-800-833-7460.

The safety and effectiveness of WAKIX have not been established in patients less than 18 years of age.

WAKIX is extensively metabolized by the liver. WAKIX is contraindicated in patients with severe hepatic impairment. Dosage adjustment is required in patients with moderate hepatic impairment.

WAKIX is not recommended in patients with end-stage renal disease. Dosage adjustment of WAKIX is recommended in patients with moderate or severe renal impairment.

Dosage reduction is recommended in patients known to be poor CYP2D6 metabolizers; these patients have higher concentrations of WAKIX than normal CYP2D6 metabolizers.

Please see the Full Prescribing Information for WAKIX for more information.

To report suspected adverse reactions, contact Harmony Biosciences, LLC at 1-800-833-7460 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

About Narcolepsy
Narcolepsy is a rare, chronic, debilitating neurologic disorder of sleep-wake state instability that impacts up to 200,000 Americans and is primarily characterized by excessive daytime sleepiness (EDS) and cataplexy – its two cardinal symptoms – along with other manifestations of REM sleep dysregulation, which intrude into wakefulness. EDS is the inability to stay awake and alert during the day and is the symptom that is present in all people living with narcolepsy. In most patients, narcolepsy is caused by the loss of hypocretin, a neuropeptide in the brain that supports sleep-wake state stability. This disorder affects men and women equally, with typical symptom onset in adolescence or young adulthood; however, it can take up to a decade to be properly diagnosed.

About Harmony Biosciences, LLC
Harmony Biosciences, LLC is a private pharmaceutical company headquartered in Plymouth Meeting, PA. The company was established in October 2017 with a vision to provide novel treatment options for people living with rare and orphan diseases, with an emphasis on central nervous system disorders, starting with patients living with narcolepsy. Harmony is committed to advancing the understanding of narcolepsy and providing information and resources to individuals who live with, and healthcare professionals who treat patients with, this disorder. For more information on Harmony Biosciences, visit www.harmonybiosciences.com.

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