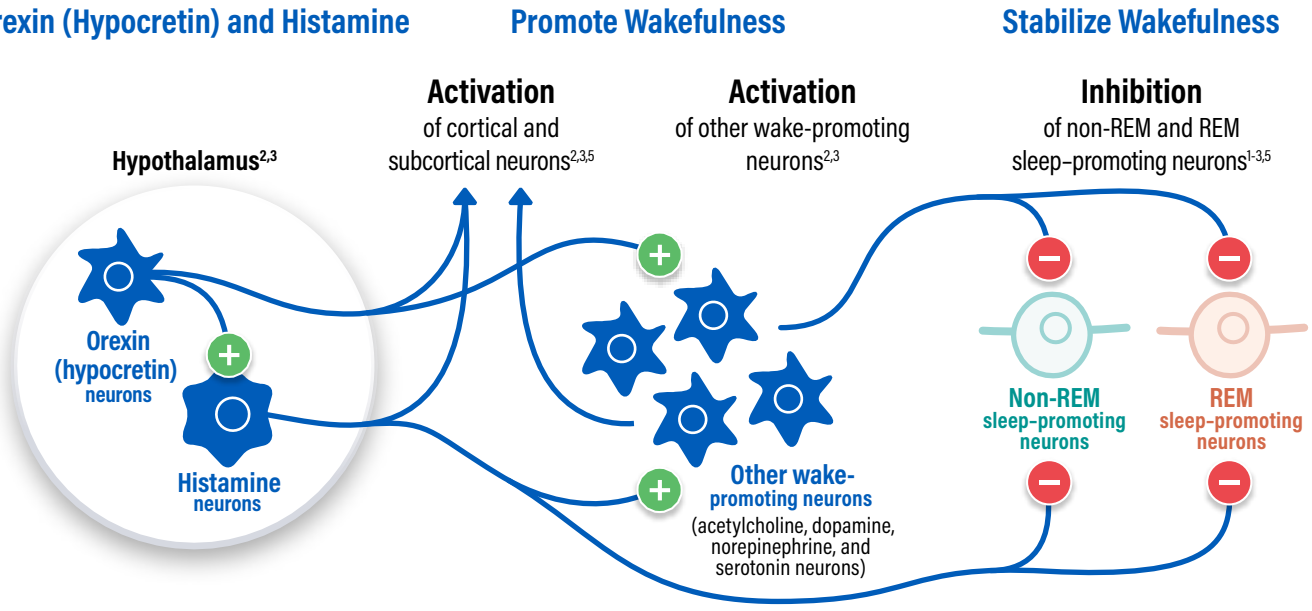
Histamine Plays an Important Role in Promoting and Stabilizing Wakefulness[1-3]

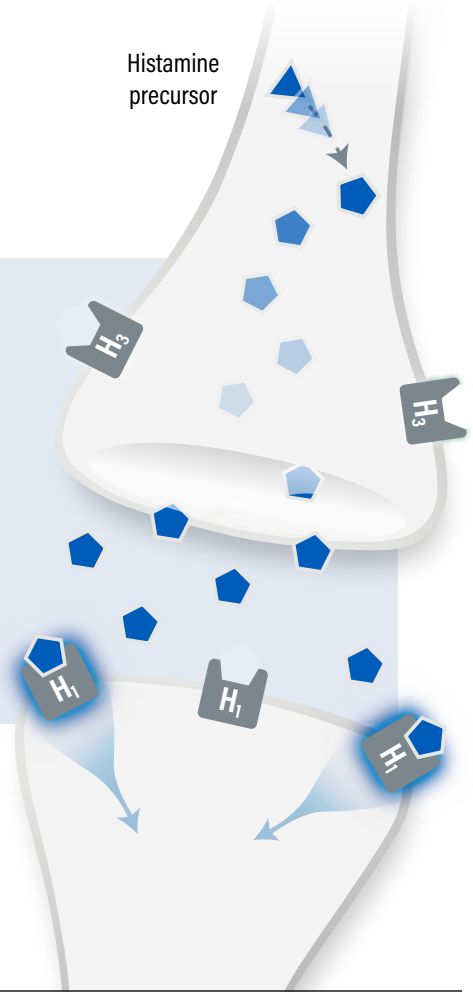
In the brain, orexin (hypocretin) and histamine neurons play complementary roles[4]

- Orexin and histamine promote wakefulness by activating the cortex and wake-promoting neurons[2,3]
- Orexin and histamine help stabilize wakefulness by inhibiting sleep-promoting neurons (non-REM and REM)[1-3]



In the brain, histamine acts as a key wake-promoting neurotransmitter[1,6]

- Histamine is synthesized in the presynaptic neuron[1]
- When released into the synapse, histamine binds to postsynaptic H_1 receptors[1]



H_1 and H_3 receptors modulate histamine neuronal activity in the brain[1]

H_3 receptors are found primarily in the brain and help regulate histamine synthesis and release[1,7-9]

- Normally, when synaptic histamine levels are high, histamine binds to H_3 autoreceptors to inhibit further synthesis and release of histamine in the brain[1,7]

H_1 receptors increase neuronal activity, which allows for communication with brain regions important for sleep and wakefulness[1,2,7]

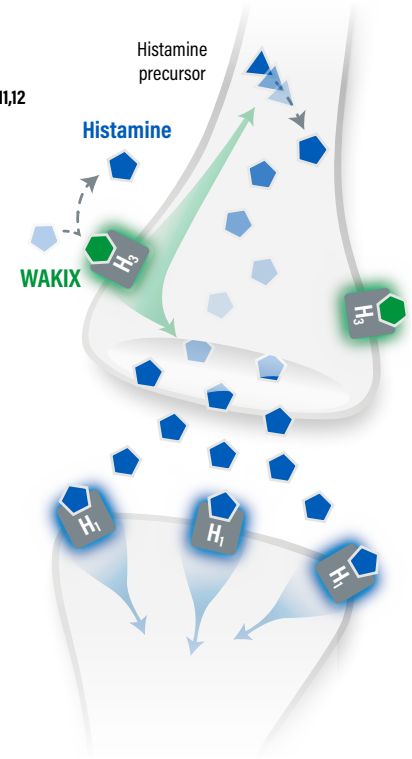
H_1, histamine 1; H_3, histamine 3.

Wakix pitolisant tablets

WAKIX Is the First and Only Histaminergic Treatment for EDS or Cataplexy in Adult Patients With Narcolepsy and for EDS in Pediatric Patients (6 Years and Older) With Narcolepsy

The mechanism of action (MOA) of WAKIX in excessive daytime sleepiness (EDS) in patients 6 years and older with narcolepsy or cataplexy in adult patients with narcolepsy is unclear; however, its efficacy could be mediated through its activity as an antagonist/inverse agonist at histamine 3 (H_3) receptors, which results in increased histamine levels in the brain.

- **WAKIX blocks histamine from binding to presynaptic H_3 autoreceptors**[7,10,11]
- **WAKIX binding to H_3 receptors increases histamine synthesis and release**[7,11,12]
- **Histamine binds to H_1 receptors, which increases communication to neurons in brain regions important for sleep and wakefulness**[13,14]



WAKIX binds to H_3 receptors with a high affinity (K_i = 1 nM) and has no appreciable binding to other histamine receptors (H_1, H_2, or H_4 receptors; K_i ≥10 µM)

H_1 receptors increase neuronal activity, which allows for communication with brain regions important for sleep and wakefulness.[1,2,7] H_3 receptors help regulate histamine synthesis and release.[7] Normally, when synaptic histamine levels are high, histamine binds to H_3 autoreceptors to inhibit further synthesis and release of histamine in the brain.[1,7]

H_1, histamine 1; H_2, histamine 2; H_4, histamine 4; K_i, inhibitory constant.

Learn more about the MOA of WAKIX at WAKIXhcp.com

Indications and Usage

- WAKIX is indicated for the treatment of excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy and for the treatment of excessive daytime sleepiness (EDS) in pediatric patients 6 years of age and older with narcolepsy.

Important Safety Information

Contraindications

- WAKIX is contraindicated in patients with known hypersensitivity to pitolisant or any component of the formulation. Anaphylaxis has been reported. WAKIX is also 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. WAKIX is contraindicated in patients with severe hepatic impairment and not recommended in patients with end-stage renal disease (ESRD).

Adverse Reactions

- In the placebo-controlled clinical trials conducted in adult patients with narcolepsy with or without cataplexy, the most common adverse reactions (≥5% and at least 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 tract infection, musculoskeletal pain, heart rate increased, hallucinations, irritability, abdominal pain, sleep disturbance, decreased appetite, cataplexy, dry mouth, and rash.
- In the placebo-controlled phase of the clinical trial conducted in pediatric patients 6 years and older with narcolepsy with or without cataplexy, the most common adverse reactions (≥5% and greater than placebo) for WAKIX were headache (19%) and insomnia (7%). The overall adverse reaction profile of WAKIX in the pediatric clinical trial was similar to that seen in the adult clinical trial program.

Please see Important Safety Information continued on next page and accompanying Full Prescribing Information.

Wakix pitolisant tablets

WAKIX Summary

Established efficacy and safety in adult and pediatric clinical studies in narcolepsy

Convenient, once-daily morning dosing

First and only histaminergic treatment for excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy and for EDS in pediatric patients (6 years and older) with narcolepsy

Not a controlled substance

No clinically important pharmacokinetic (PK) interactions with modafinil or sodium oxybate demonstrated in a clinical PK study in adults[15]

Important Safety Information

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.
- H_1 receptor antagonists that cross the blood-brain barrier may reduce the effectiveness of WAKIX. Patients should avoid centrally acting H_1 receptor antagonists.
- WAKIX is a borderline/weak inducer of CYP3A4. WAKIX may reduce the effectiveness of sensitive CYP3A4 substrates, including 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.

Visit WAKIXhcp.com for resources and to download the WAKIX Prescription Referral Form

Use in Specific Populations

- 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 for the treatment of excessive daytime sleepiness in pediatric patients less than 6 years of age with narcolepsy. The safety and effectiveness of WAKIX have not been established for the treatment of cataplexy in pediatric patients with narcolepsy.
- 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 eGFR <60 mL/minute/1.73 m^2.
- Dosage reduction is recommended in patients known to be poor CYP2D6 metabolizers; these patients have higher concentrations of WAKIX than normal CYP2D6 metabolizers.

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

References

1. Scammell TE et al. *Sleep*. 2019;42(1). doi:10.1093/sleep/zsy183 **2.** Scammell TE et al. *Neuron*. 2017;93(4):747-765. **3.** Haas HL et al. *Physiol Rev*. 2008;88(3):1183-1241. **4.** Anaclet C et al. *J Neurosci*. 2009;29(46):14423-14438. **5.** Saper CB et al. *Neuron*. 2010;68(6):1023-1042. **6.** España RA, Scammell TE. *Sleep*. 2011;34(7):845-858. **7.** Nieto-Alamilla G et al. *Mol Pharmacol*. 2016;90(5):649-673. **8.** Panula P et al. *Pharmacol Rev*. 2015;67(3):601-655. **9.** Schlicker E, Kathmann M. *Handb Exp Pharmacol*. 2017;241:277-299. **10.** Ligneau X et al. *J Pharmacol Exp Ther*. 2007;320(1):365-375. **11.** Schwartz J-C. *Br J Pharmacol*. 2011;163(4):713-721. **12.** Stahl SM. In: *Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 2nd ed. Cambridge University Press; 2000:77-98. **13.** Benarroch EE. *Neurology*. 2010;75(16):1472-1479. **14.** Lin J-S et al. *J Pharmacol Exp Ther*. 2011;336(1):17-23. **15.** Data on file. Harmony Biosciences.

HARMONY BIOSCIENCES