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Suvorexant

Updated: February 20, 2018.

OVERVIEW

Introduction

Suvorexant is an orexin receptor antagonist used for the treatment of insomnia and sleep disorders. Suvorexant therapy is associated with rare occurrence of transient serum enzyme elevations, but has not been implicated in cases of clinically apparent liver injury.

Background

Suvorexant (soo" voe rex' ant) is an orexin receptor antagonist which is used to treat insomnia. Central nervous system neurons with orexin receptors are involved in wakefulness and are inactive during sleep. Engagement of the orexin receptor results in wakefulness, and loss of the receptor can result in excessive daytime sleepiness and narcolepsy. Inhibition of orexin receptor signaling using suvorexant has been shown to shorten the time to falling asleep and to prolong sleep in patients with sleep-onset and sleep-maintenance insomnia. Suvorexant was approved for use in the United States in 2014, the first such orexin based drug approved for insomnia. Suvorexant is available in 5, 10, 15 and 20 mg tablets under the brand name Belsomra. The recommended dose is 10 mg taken orally within 30 minutes of bedtime. The dose can be increased to 20 mg. Side effects are few, but may include daytime somnolence, fatigue, dizziness, headache and vivid or abnormal dreams.

Hepatotoxicity

In several clinical trials, suvorexant was found to be well tolerated, with serum ALT elevations in 0 to 5% of patients, usually with higher doses, and resolving spontaneously without dose modification. In the registration trials of suvorexant, there were no reports of clinically apparent liver injury. Suvorexant has been available for a limited period of time, but has yet to be implicated in causing clinically apparent liver injury.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which suvorexant might cause liver injury is unknown. Suvorexant is metabolized by the cytochrome P450 system (predominantly CYP3A4) and the dose may need to be altered in patients taking strong inhibitors (decreasing dose) or inducers (increasing dose) of the enzymes. The relative lack of serious liver related adverse events is probably due to the low doses used and its uncommon, intermittent use.

Drug Class: Sedatives and Hypnotics, Miscellaneous

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Suvorexant – Belsomra®

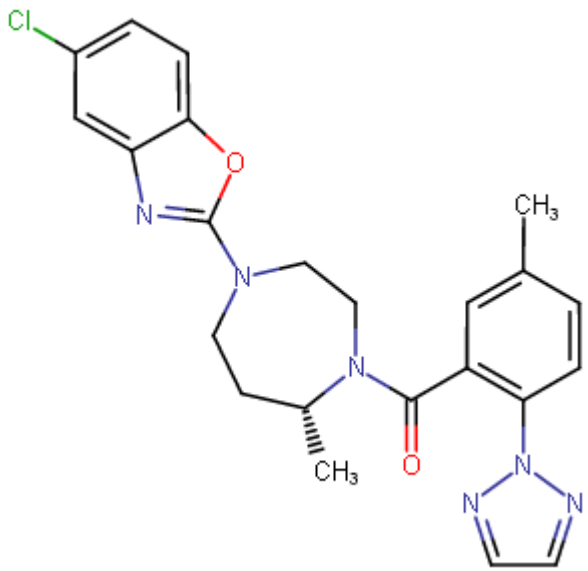
DRUG CLASS

Sedatives and Hypnotics

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Suvorexant	1030377-33-3	**C23-H23-Cl-N6-O2**	

ANNOTATED BIBLIOGRAPHY

References updated: 20 February 2018

Zimmerman HJ. Unconventional drugs. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 731-4.

(Expert review of hepatotoxicity published in 1999; suvorexant and the orexin receptor antagonists are not discussed).

Larrey D, Ripault MP. Anxiolytic agents. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, p. 455-6.

(Review of hepatotoxicity of hypnotics and sedatives discusses benzodiazepines, buspirone and valerian, all of which have been linked to rare cases of liver injury; suvorexant and orexin receptor antagonists are not discussed).

Mihic SJ, Harris RA. Hypnotics and sedatives. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 457-80.

(Textbook of pharmacology and therapeutics).

Herring WJ, Snyder E, Budd K, Hutzelmann J, Snavely D, Liu K, Lines C, et al. Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. Neurology 2012; 79: 2265-74. PubMed PMID: 23197752.

(Among 254 patients treated with one of 4 doses of suvorexant or placebo in a cross over design, adverse events were more common with higher doses and consisted mainly of somnolence [2-12%], headache [0-5%], dizziness [0-5%] and abnormal dreams [0-5%], with rare instances of ALT elevations [1.6-3.4% with higher doses vs 0.4% with placebo], all of which resolved spontaneously without dose modification).

Herring WJ, Connor KM, Ivgy-May N, Snyder E, Liu K, Snavely DB, Krystal AD, et al. Suvorexant in patients with insomnia: results from two 3-month randomized controlled clinical trials. Biol Psychiatry 2014 Oct 23. [Epub ahead of print] PubMed PMID: 25526970.

(In two 3-month controlled trials of suvorexant versus placebo for primary insomnia in 2040 patients, "No clinically relevant changes in laboratory … measures were observed" and no serious hepatic adverse events were reported).

Michelson D, Snyder E, Paradis E, Chengan-Liu M, Snavely DB, Hutzelmann J, Walsh JK, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol 2014; 13: 461-71. PubMed PMID: 24680372.

(Among 522 patients with insomnia treated with suvorexant or placebo for one year, rates of adverse events with similar in the two groups and "there were no clinically meaningful differences between groups in vital signs or laboratory values").

Yin J, Mobarec JC, Kolb P, Rosenbaum DM. Crystal structure of the human OX (2) orexin receptor bound to the insomnia drug suvorexant. Nature 2014 Dec 22. [Epub ahead of print] PubMed PMID: 25533960.

(Resolution of the crystal structure of the human orexin receptor bound to suvorexant).

Suvorexant (Belsomra) for insomnia. Med Lett Drugs Ther 2015; 57 (1463): 29-31. PubMed PMID: 25719996.

(Concise review of the efficacy, safety and costs of suvorexant as therapy of insomnia shortly after its approval in the US, mentions the most common side effect as being next day somnolence [in 7-13% of recipients]; no mention of hepatotoxicity or ALT elevations).

Patel KV, Aspesi AV, Evoy KE. Suvorexant: A dual orexin receptor antagonist for the treatment of sleep onset and sleep maintenance insomnia. Ann Pharmacother 2015 Feb 9. [Epub ahead of print] PubMed PMID: 25667197.

(Review of 3 randomized, controlled trials of suvorexant as therapy of insomnia mentions that somnolence, fatigue and headache were more common with drug than placebo; no mention of ALT elevations or hepatotoxicity).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 82 [9%] were attributed to agents active in the central nervous system, but none were sedatives or sleeping aids).

Drugs for insomnia. Med Lett Drugs Ther 2015; 57 (1472): 95-8. PubMed PMID: 26147892.

(Concise review of the mechanism of action, efficacy, safety and costs of drugs for insomnia including benzodiazepine receptor agonists, benzodiazepines, melatonin receptor agonists, orexin receptor antagonists such as suvorexant and other agents including nonprescription and herbal products; no mention of ALT elevations or hepatotoxicity).

Schroeck JL, Ford J, Conway EL, Kurtzhalts KE, Gee ME, Vollmer KA, Mergenhagen KA. Review of safety and efficacy of sleep medicines in older adults. Clin Ther 2016; 38: 2340-72. PubMed PMID: 27751669.

(Systematic review of the literature on the safety and efficacy of sleep aids in the elderly focuses upon common adverse events such as somnolence, fatigue, headache and dry mouth with special emphasis on dementia, forgetfulness, daytime somnolence, falls and fractures; no mention of ALT elevations or hepatotoxicity).

Kuriyama A, Tabata H. Suvorexant for the treatment of primary insomnia: A systematic review and meta-analysis. Sleep Med Rev 2017; 35: 1-7. PubMed PMID: 28365447.

(Systematic review of the safety and efficacy of suvorexant does not mention effects on ALT levels or hepatotoxicity).