NEW DRUG APPROVAL

Brand Name	Quviviq™
Generic Name	daridorexant
Drug Manufacturer	Idorsia Pharmaceuticals US Inc.

New Drug Approval

FDA approval date: January 7, 2022

Review designation: Standard

Type of review: Type 1 - New Molecular Entity; New Drug Application (NDA): 214985

Dispensing restriction: Open distribution

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Insomnia is a common sleep complaint that occurs when you have one or more of these problems:

- You have a hard time initiating sleep.
- You struggle to maintain sleep, waking up frequently during the night.
- You tend to wake up too early and are unable to go back to sleep.
- You sleep is nonrestorative or of poor quality.

These symptoms of insomnia can be caused by a variety of biological, psychological, and social factors. They most often result in an inadequate amount of sleep, even though the sufferer has the opportunity to get a full night of sleep. Insomnia is different from sleep deprivation, which occurs when an individual does not have the opportunity to get a full night of sleep. A small percentage of people who have trouble sleeping are short sleepers who can function normally on only five hours of sleep or less. There are two types of insomnia – primary and secondary. Primary insomnia is sleeplessness that cannot be attributed to an existing medial, psychiatric, or environmental cause (such as drug abuse or medications). Secondary insomnia is when symptoms of insomnia arise from a primary medical illness, mental disorders, or other sleep disorders. It may also arise from the use, abuse or exposure to certain substances.

Approximately 30% to 40% of adults in the United States report symptoms of insomnia at some point in a given year. Short-term insomnia has an estimated prevalence of 9.5% in the United States, but about 1 in 5 cases of short-term insomnia transitions to chronic insomnia, which can persist for years. In longitudinal studies, insomnia continued in 40% to 70% of patients for as long as 4 years. Although symptoms persist in some patients, insomnia may have a waxing and waning course in others.

The incidence of insomnia appears to be increasing in the United States. Based on National Health Interview Survey data, the unadjusted prevalence of insomnia or trouble sleeping increased by 8% over a decade, from 17.5% (37.5 million adults) in 2002 to 19.2% (46.2 million adults) in 2012. National Ambulatory Medical Care Survey data showed that the number of office visits for insomnia increased by 13% over 10 years, from 4.9 million visits in 1999 to 5.5 million visits in 2010.Based on Medicare data, physician-diagnosed insomnia increased from 3.9% in 2006 to 6.2% in 2013.

- 30% to 50% of the U.S. population experiences occasional, short-term insomnia.
- Prevalence of chronic insomnia disorder in industrialized nations is estimated to be at least 5% to 10%.

- Prevalence is significantly higher in medically and psychiatrically ill populations, as well as in older adults (65 years of age and older).

Efficacy

Quviviq™ was evaluated in two 3-month multicenter, randomized, double-blind, placebo-controlled, parallel-group studies, Study 1 (NCT03545191) and Study 2 (NCT03575104), as well as a 9-month extension study, Study 3 (NCT03679884). Study 1 evaluated a 50-mg and 25-mg dose of Quviviq™ or placebo in 930 participants. Study 2 evaluated a 25-mg and 10-mg dose of Quviviq™ or placebo in 924 participants (the 10-mg dose is not approved by the FDA). Both studies included a 7-day placebo run-out period, after which patients could enter the extension study.

Table 1. Quviviq™ Study 1 and Study 2 Summary

	Study 1 (NCT03545191)	Study 2 (NCT03575104)
Design	Double-blind, randomized, placebo-controlled, parallel-group, polysomnography study	Double-blind, randomized, placebo-controlled, parallel-group, polysomnography study

Study Population	• 930 patients with insomnia disorder per *DSM-5* criteria and ISI score ≥15
	• Median age: 55.4 years (range, 18–88 years)
	  ○ 39.1% ≥65 years of age, including 5.8% ≥75 years of age
	• 67.1% female
	  ○ 90% White
	  ○ 8% Black or African American
	  ○ 1% Asian
	  ○ <1% Other
	Key Exclusion Criteria: Lifetime history of related breathing disorder, periodic limb movement disorder, restless legs syndrome, circadian rhythm disorder, REM behavior disorder, narcolepsy, or apnea/hypopnea
		• 924 patients with insomnia disorder per DSM-5 and ISI score ≥15
		• Median age: 56.7 years (range, 19–85 years)
		  ○ 39.3% ≥65 years of age, including 6.1% ≥75 years of age
		• 69% female
		  ○ 88% White
		  ○ 8% Black or African American
		  ○ 4% Asian
		  ○ <1% Other
		Key Exclusion Criteria: Lifetime history of related breathing disorder, periodic limb movement disorder, restless legs syndrome, circadian rhythm disorder, REM behavior disorder, narcolepsy, or apnea/hypopnea

Interventions	Patients were randomized to receive Quviviq™ 50 mg (n = 310), Quviviq™ 25 mg (n = 310), or placebo (n = 310) for 3 months	Patients were randomized to receive Quviviq™ 25 mg (n = 309), Quviviq™ 10 mg[a] (n = 307), or placebo (n = 308) for 3 months

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Endpoints	• **Primary endpoints**: Change from baseline to Month 1 and Month 3 in LPS and WASO • **Key secondary endpoints:** Patient-reported sTST evaluated every morning at home using a validated sleep diary questionnaire	• **Primary endpoints:** Change from baseline to Month 1 and Month 3 in LPS and WASO • **Key secondary endpoints:** Patient-reported sTST evaluated every morning at home using a validated sleep diary questionnaire

Efficacy Results	Month 3, change from baseline, LSM (95% CL)
	• Quviviq™ 25 mg
	  ○ WASO, minutes: –23 (–27, –19)
	  ○ LPS, minutes: –31 (–34, –27)
	  ○ sTST, minutes: 48 (41, 54)
	• Quviviq™ 50 mg
	  ○ WASO, minutes: –29 (–33, –25)
	  ○ LPS, minutes: –35 (–38, –31)
	  ○ sTST, minutes: 58 (51, 64)
	• Placebo
	  ○ WASO, minutes: –11 (–15, –7)
	  ○ LPS, minutes: –23 (–26, -20)
	  ○ sTST, minutes: 38 (31, 44)
	Month 3, difference to placebo, LSM (95% CL)
	• Quviviq™ 25 mg
	  ○ WASO, minutes: –12 (–17, –6)b
	  ○ LPS, minutes: –8 (–12, –3)b
	  ○ sTST, minutes: 10 (1, 19)b
	• Quviviq™ 50 mg
	  ○ WASO, minutes: –18 (–24, –13)b
	  ○ LPS, minutes: –12 (–16, –7)b
	  ○ sTST, minutes: 20 (11, 29)b
		Month 3, change from baseline, LSM (95% CL)
		• Quviviq™ 25 mg
		  ○ WASO, minutes: –24 (–29, –19)
		  ○ LPS, minutes: –29 (–33, –24)
		  ○ sTST, minutes: 56 (50, 63)
		• Placebo
		  ○ WASO, minutes: –14 (–19, –9)
		  ○ LPS, minutes: –20 (–24, –15)
		  ○ sTST, minutes: 37 (31, 43)
		Month 3, difference to placebo, LSM (95% CL)
		• Quviviq™ 25 mg
		  ○ WASO, minutes: –10 (–17, –4)b
		  ○ LPS, minutes: –9 (–15, –3)
		  ○ sTST, minutes: 19 (10, 28)b

Safety Results	Adverse reactions reported in ≥2% of Quviviq™ patients and greater than placebo patients in Study 1 • Headache (Quviviq™ 25 mg: 6%; Quviviq™ 50 mg: 7%; placebo: 5%) • Somnolence or fatigue (Quviviq™ 25 mg: 6%; Quviviq™ 50 mg: 5%; placebo: 4%) • Dizziness (Quviviq™ 25 mg: 2%; Quviviq™ 50 mg: 3%; placebo: 2%) • Nausea (Quviviq™ 25 mg: 0%; Quviviq™ 50 mg: 3%; placebo: 2%) Geriatric use • Chance of somnolence and fatigue increased with age. The prescribing information notes that because it can increase somnolence and drowsiness, elderly patients are at higher risk of falls.	

Safety

ADVERSE EVENTS

The safety of Quviviq™ was evaluated in three placebo-controlled clinical studies (two 3-month studies of identical design [Study 1 and Study 2], and a 9-month extension study [Study 3]). Study 1 evaluated 50 mg and 25 mg doses of Quviviq™, while Study 2 evaluated a 25 mg dose and a 10 mg dose of Quviviq™. The 10 mg dose is not an approved dose. A total of 1232 patients (including approximately 40% elderly patients [> 65 years old]), received Quviviq™ 50 mg (N = 308); 25 mg (N = 618); or 10 mg (an unapproved dose) (N = 306). A total of 576 patients were treated with Quviviq™ for at least 6 months and 331 for at least 12 months. Function.

Table 2: Adverse Reactions Reported in ≥ 2% of Quviviq™-treated Patients and Greater than in Placebo-treated Patients in a 3-Month Placebo-Controlled Study (Study 1)

	QUVIVIQ 25 mg (N=310) %	QUVIVIQ 50 mg (N=308) %	Placebo (N=309) %
Nervous System Disorders			
Headache*	6	7	5
Somnolence or fatigue*	6	5	4
Dizziness*	2	3	2
Gastro-intestinal disorders			
Nausea*	0	3	2

*The following terms were combined:
Headache includes: headache, tension headache, migraine, migraine with aura, head discomfort
Somnolence or fatigue includes: somnolence, sedation, fatigue, hypersomnia, lethargy
Dizziness includes: dizziness, vertigo, labyrinthitis
Nausea includes: nausea, vomiting, procedural nausea

Other Adverse Reactions Observed During Clinical Trials (Study 1 and Study 2) Other adverse reactions of < 2% frequency but greater than placebo are mentioned below.

The following do not include adverse reactions 1) for which a drug cause was remote, 2) that were so general as to be uninformative, or 3) that were not considered to have clinically significant implications. Reference ID: 4916652
• Sleep paralysis was reported in 0.5% and 0.3% of patients receiving Quviviq™25 mg and 50 mg, respectively, compared to no reports for placebo.

• Hypnagogic and hypnopompic hallucinations were reported in 0.6% of patients receiving Quviviq™ 25 mg compared to no cases with Quviviq™ 50 mg or placebo.

WARNINGS & PRECAUTIONS

CNS-Depressant Effects and Daytime Impairment

Quviviq™ is a central nervous system (CNS) depressant that can impair daytime wakefulness even when used as prescribed. CNS-depressant effects may persist in some patients for up to several days after discontinuing Quviviq™. Prescribers should advise patients about the potential for next-day somnolence. Driving ability was impaired in some subjects taking Quviviq™ 50 mg. The risk of daytime impairment is increased if Quviviq™ is taken with less than a full night of sleep remaining or if a higher than recommended dose is taken. If Quviviq™ is taken in these circumstances, caution patients against driving and other activities requiring complete mental alertness. Co-administration with other CNS depressants (e.g., benzodiazepines, opioids, tricyclic antidepressants, alcohol) increases the risk of CNS depression, which can cause daytime impairment. Dosage adjustments of Quviviq™ and of concomitant CNS depressants may be necessary when administered together because of potentially additive effects. The use of Quviviq™ with other drugs to treat insomnia is not recommended. Advise patients not to

consume alcohol in combination with Quviviq™ because co-administration of Quviviq™ with alcohol resulted in additive effects on psychomotor performance. Because Quviviq™ can cause drowsiness, patients, particularly the elderly, are at a higher risk of falls.

Worsening of Depression/Suicidal Ideation

Patients with psychiatric disorders, including insomnia, are at increased risk of suicide. In primarily depressed patients treated with hypnotics, worsening of depression and suicidal thoughts and actions (including completed suicides) have been reported. As with other hypnotics, Quviviq™ should be administered with caution in patients exhibiting symptoms of depression. Monitoring of suicide risk and protective measures may be required.

Sleep Paralysis, Hypnagogic/Hypnopompic Hallucinations, and Cataplexy-like Symptoms

Sleep paralysis, an inability to move or speak for up to several minutes during sleep-wake transitions, and hypnagogic/hypnopompic hallucinations, including vivid and disturbing perceptions, can occur with the use of Quviviq™.Prescribers should explain the nature of these events to patients when prescribing Quviviq™.

Symptoms similar to mild cataplexy have been reported with orexin receptor antagonists. Such symptoms can include periods of leg weakness lasting from seconds to a few minutes, can occur either at night or during the day, and may not be associated with an identified triggering event (e.g., laughter or surprise).

Complex Sleep Behaviors

Complex sleep behaviors, including sleepwalking, sleep-driving, and engaging in other activities while not fully awake (e.g., preparing and eating food, making phone calls, having sex), have been reported to occur with the use of hypnotics, including orexin receptor antagonists such as Quviviq™. These events can occur in hypnotic-naïve as well as in hypnotic-experienced persons. Patients usually do not remember these events. Complex sleep behaviors may occur following the first or any subsequent use of hypnotics, such as Quviviq™, with or without the concomitant use of alcohol and other CNS depressants. Discontinue Quviviq™ immediately if a patient experiences a complex sleep behavior.

Patients with Compromised Respiratory Function

The effects of Quviviq™ on respiratory function should be considered if prescribed to patients with compromised respiratory function. Quviviq™ has not been studied in patients with moderate OSA requiring CPAP or severe OSA. QUVIVIQ has not been studied in patients with severe COPD.

Need to Evaluate for Co-morbid Diagnoses

Because sleep disturbances may be the presenting manifestation of a medical and/or psychiatric disorder, treatment of insomnia should be initiated only after careful evaluation of the patient. The failure of insomnia to remit after 7 to 10 days of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia or the emergence of new cognitive or behavioral abnormalities may be the result of an unrecognized underlying psychiatric or medical disorder and can emerge during the course of treatment with sleep-promoting drugs such as Quviviq™.

CONTRAINDICATIONS

Quviviq™ is contraindicated in patients with narcolepsy.

Clinical Pharmacology

MECHANISMS OF ACTION

The mechanism of action of daridorexant in the treatment of insomnia is presumed to be through antagonism of orexin receptors. The orexin neuropeptide signaling system plays a role in wakefulness. Blocking the binding of

wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress wake drive.

Dose & Administration

ADULTS

25 mg to 50 mg once per night, taken orally within 30 minutes before going to bed, with at least 7 hours remaining prior to planned awakening.

PEDIATRICS

The safety and effectiveness of Quviviq™ have not been established in pediatric patients.

GERIATRICS

No dose adjustment is required in patients over the age of 65 years.
Quviviq™ can increase somnolence and drowsiness, patients, particularly the elderly, are at higher risk of falls.

RENAL IMPAIRMENT

N/A

HEPATIC IMPAIRMENT

- Moderate hepatic impairment: Maximum recommended dosage is 25 mg no more than once per night.
- Severe hepatic impairment: Not recommended.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Tablets: 25 mg, 50 mg