Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Daridorexant

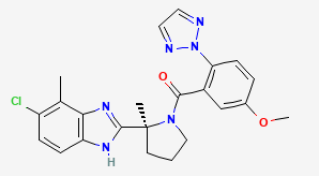
Evidence Summary

Daridorexant improves induction and maintenance of sleep in people with insomnia. Common adverse events include headache, somnolence and fatigue. Long-term safety beyond 1 year has not been studied.

Neuroprotective Benefit: Daridorexant improves sleep parameters in people with insomnia, which in turn may benefit brain health. No clinical data on neuroprotection exist to date. A clinical study is ongoing in people with MCI/AD and insomnia.

Aging and related health concerns: Daridorexant treatment improves 'latency to persistent sleep', 'wake time after sleep onset', and total sleep time in people with insomnia.

Safety: Common adverse events include headache, somnolence, and fatigue. Daridorexant may have a better safety profile than other insomnia medications, but it may increase the risk of CNS depressant effects, daytime impairment, sleep paralysis, and others.

Availability: Rx for insomnia	**Dose**: The recommended dose for adults with insomnia is 25 to 50 mg, once per night, orally. The maximum dose is 50 mg per night.	**Chemical formula:** $C_{23}H_{23}ClN_6O_2$ **MW**: 450.9  Source: PubChem
Half-life: terminal half-life is approximately 8 hours	**BBB**: penetrant	
Clinical trials: A meta-analysis of 7 randomized controlled trials included a total of 2,425 people with insomnia.	**Observational studies**: N/A	

What is it?

Daridorexant is a selective dual orexin receptor antagonist used to treat insomnia in adults. Orexin is a wake-promoting neuropeptide produced in the hypothalamus. Orexin neurons originating in the lateral hypothalamic area and posterior hypothalamus regulate sleep and wakefulness by sending excitatory projections to monoaminergic and cholinergic nuclei in the brain stem and hypothalamic regions, including the locus coeruleus (containing noradrenaline), tuberomammilary nucleus (containing histamine), raphe nuclei (containing serotonin), and laterodorsal/pedunclopontine tegmental nuclei (containing acetylcholine)(reviewed in Sakurai 2007). The binding of orexin A and orexin B at orexin receptors OX1R and OX2R activates these neurons and promotes alertness (Mieda et al., 2013). These neurons remain dormant in sleep. Daridorexant blocks the binding of orexins at OX1R and OX2R (drugbank.com). Daridorexant was selected from a pool of drug candidates based on an expected efficacy duration of ~8 hours, with a half-life (8 hours) targeted to minimize next-morning residual effects.

In January 2022, daridorexant was approved by the FDA for the treatment of insomnia. Daridorexant was the second orexin receptor antagonist approved to treat insomnia following suvorexant. Daridorexant is also approved in Europe and Canada.

Neuroprotective Benefit: Daridorexant improves sleep parameters in people with insomnia, which in turn may benefit brain health. No clinical data on neuroprotection exist to date. A clinical study is ongoing in people with MCI/AD and insomnia.

Types of evidence:

- 0 clinical trials with daridorexant
- Several clinical studies of other orexin receptor antagonists
- Several reviews of the use of orexin receptor antagonists for the prevention and treatment of Alzheimer's disease and associated sleep disorders

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No clinical trials or observational studies have evaluated whether daridorexant prevents dementia or age-related cognitive decline.

Chronic sleep problems may directly contribute to risk of Alzheimer's disease by impairing glymphatic clearance of Aβ and other toxic proteins from the brain (Sprecher et al., 2017; Xie et al., 2013). In cognitively normal older adults, Aβ burden in the medial prefrontal cortex correlated with the severity of impairment in non-REM slow wave activity, and impaired non-REM slow wave activity was associated with impaired overnight memory consolidation (Mander et al., 2015). Thus, for people who do not get appropriate length or quality of sleep, improving these measures (behaviorally or pharmacologically) may theoretically affect cognitive function and future dementia risk.

Human research to suggest benefits to patients with dementia:

Sleep and circadian sleep-wake cycle disruptions are prevalent in people with Alzheimer's disease and other dementias (reviewed in Carpi et al., 2024). Sleep disruption may increase brain deposition of Aβ and other toxic proteins, which in turn may further impair sleep, contributing to disease progression.

In a 2021 meta-analysis of 17 studies, cerebrospinal fluid (CSF) levels of orexin were non-significantly increased in people with Alzheimer's disease compared to controls, with moderate to large heterogeneity among studies (Treu and Plante, 2021).

Clinical studies of other orexin receptor antagonists (e.g., suvorexant, lemborexant) have shown enhancement of sleep quality in patients with Alzheimer's disease and sleep or circadian sleep-wake rhythm disorders (reviewed in Carpi et al., 2024). While there are no completed studies of daridorexant in people with dementia as of November 2024, there is an ongoing phase IV randomized crossover clinical trial (DARIDOR-ALZ) that is evaluating the efficacy and safety of daridorexant (50 mg per night) in 62 people with mild cognitive impairment or mild-to-moderate Alzheimer's patients with insomnia complaints (NCT05924425). This study is scheduled to be completed in March 2027.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

No studies have directly tested the potential neuroprotective effects of daridorexant in laboratory or clinical studies.

In cognitively unimpaired adults (45-65 years old), administration of suvorexant (20 mg), a different dual orexin receptor antagonist, decreased CSF ptau181/tau181 ratio by 10-15% compared to placebo (Lucey et al., 2023). Suvorexant treatment also decreased CSF Aβ42 by 10-20%.

APOE4 interactions: Unknown

Aging and related health concerns: Daridorexant treatment improves 'latency to persistent sleep', 'wake time after sleep onset', and total sleep time in people with insomnia.

Types of evidence:

- 4 meta-analyses or systematic reviews
- 8 double-blind randomized controlled clinical trials
- Numerous posthoc analyses of the phase 3 trials
- 2 open-label studies
- Clinical guidelines for insomnia
- Numerous reviews

Insomnia: IMPROVES INDUCTION AND MAINTENANCE OF SLEEP

The first-line treatment for chronic insomnia in adults is cognitive behavioral therapy (Riemann et al., 2023). However, when cognitive behavioral therapy for insomnia is not sufficiently effective, a pharmacological intervention is offered. Medications are initially prescribed for the short-term (up to 4 weeks), including benzodiazepines, benzodiazepine receptor agonists, orexin receptor antagonists, and low-dose sedating antidepressants. Benefits with these drugs need to be weighed against the potential harms, including dependency, sedation, risks of falls/injuries, alteration in sleep architecture, and next-morning sleepiness. Dual orexin receptor antagonists can be used for periods of up to 3 months or longer (up to 1 year) in some cases.

In a 2023 meta-analysis of 7 randomized controlled trials including a total of 2,425 people with insomnia, daridorexant treatment for up to 3 months was superior to placebo in reducing 'wake time after sleep onset' (MD=-13.26; 95% CI, -15.48 to -11.03; p<0.00001) and 'latency to persistent sleep' (MD=-7.23; 95% CI, -9.60 to -4.85; p<0.00001), and increasing total sleep time (MD=14.80; 95% CI, 11.18 to 18.42; p<0.00001) and subjective total sleep time (MD=14.80; 95% CI, 11.18 to 18.42; p<0.00001)(Albadrani et al., 2023). Of the tested doses of daridorexant (5, 10, 25, or 50 mg, nightly, orally), the 25 mg and 50 mg doses were the most efficacious. Significant reductions in 'wake time after sleep onset' compared to placebo was evident as early as days 1 and 2 at the 10 mg (MD=-13.48; p=0.005), 25 mg (MD=-21.72; p=0.001), and 50 mg doses (MD=-35.50; p=0.0008). After 1 month of treatment, 'wake time after sleep onset' was significantly reduced compared to placebo for the 25 mg and 50 mg doses of daridorexant, but not for the 10 mg dose.

In a 2023 meta-analysis of 4 randomized controlled trials including a total of 2,768 people with insomnia (1,962 people randomized to daridorexant), similar benefits of daridorexant on 'wake time after sleep onset', 'latency to persistent sleep', and subjective total sleep time were observed (Dutta et al., 2023).

In another 2023 meta-analysis of 4 randomized controlled trials including a total of 2,227 people with insomnia disorder, the 50 mg nightly dose of daridorexant for 3 months was superior to placebo for 4 efficacy outcomes: wake time after sleep onset, latency to persistent sleep, subjective total sleep time, and Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) domain score (p<0.05)(Jiang et al., 2023). Self-reported total sleep time was significantly increased compared to placebo with both the 25 mg and 50 mg doses of daridorexant (p<0.001 and p=0.003, respectively).

Two multicenter randomized double-blind placebo-controlled phase 3 trials that took place at 156 sites in 17 countries enrolled a total of 1854 people with insomnia disorder (930 participants in Study 1, 924 in Study 2)(Mignot et al., 2022). In Study 1, daridorexant doses of 25 mg and 50 mg nightly were tested

against placebo. In Study 2, daridorexant doses of 10 mg and 25 mg nightly were tested against placebo. In Study 1, 'wake time after sleep onset' and 'latency to persistent sleep' were significantly reduced with the 50 mg dose of daridorexant compared to placebo at 1 month (-22.8 min, p<0.0001 for WASO; -11.4 min, p<0.0001 for LPS) and 3 months (-18.3 min, p<0.0001 for WASO; -11.7 min, p<0.0001 for LPS). Similarly, at the 25 mg dose, 'wake time after sleep onset' and 'latency to persistent sleep' were significantly reduced compared to placebo at 1 month (-12.2 min, p<0.0001 for WASO; -8.3 min, p=0.0005 for LPS) and 3 months (-11.9 min, p<0.0001 for WASO; -7.6 min, p=0.0015 for LPS). Compared with placebo, participants in the daridorexant 50 mg group had significantly improved self-reported total sleep time at 1 month (+22.1 min, p<0.0001) and 3 months (+19.8 min, p<0.0001), and IDSIQ sleepiness domain scores at 1 month (p<0.0001) and 3 months (p=0.0002). Compared with the placebo group, participants in the daridorexant 25 mg group had significantly improved self-reported total sleep time at 1 month (+12.6 min, p=0.0013) and 3 months (+9.9 min, p=0·033), but not IDSIQ sleepiness domain scores (p=0.055 at 1 month; p=0.053 at 3 months). In Study 2, 'wake time after sleep onset' was significantly reduced among participants in the daridorexant 25 mg group compared with placebo control at 1 month (-11.6 min, p=0.0001) and 3 months (-10.3 min, p=0.0028), but there were no significant differences in 'latency to persistent sleep' at 1 or 3 months. Compared with the placebo group, participants in the daridorexant 25 mg group had significant improvement in self-reported total sleep time at 1 month (+16.1 min, p<0.0001) and 3 months (+19.1, p<0.0001), but not in IDSIQ sleepiness domain scores. Compared with the placebo group, no significant differences were observed among participants in the daridorexant 10 mg group for 'wake time after sleep onset', 'latency to persistent sleep', self-reported total sleep time, or IDSIQ sleepiness domain scores at 1 or 3 months. The proportion of sleep time spent in each sleep stage was preserved across all treatment groups.

In a secondary analysis of the phase 3 trial (Study 1), efficacy of daridorexant was compared between older patients (≥65 years) and younger patients (under 65 years)(Fietze et al., 2022). Older and younger patients had similar reductions in 'wake time after sleep onset' and 'latency to persistent sleep', and similar increases in self-reported total sleep time with daridorexant treatment, with numerically greater improvements with the 50 mg dose compared to the 25 mg dose. Daridorexant at the 25 mg dose improved IDSIQ scores, but only in younger adults. Thus, older patients show clinically greater benefit with the 50 mg dose compared to the 25 mg dose.

In a long-term follow-up of the two phase 3 trials, 550 patients with insomnia completed a total of 52 weeks of intervention (daridorexant 10/25/50 mg nightly or placebo for 12 weeks, followed by a 40-week double-blind controlled extension, then a 7-day placebo run-out)(Kunz et al., 2023). Improvements in sleep and daytime functioning were maintained through to the end of the study and were most

pronounced with the 50 mg dose of daridorexant. Daridorexant at the 50 mg dose, compared with placebo, increased self-reported total sleep time by 20.4 min, 15.8 min, and 17.8 min, and decreased (i.e., improved) IDSIQ total scores by -9.3, -9.5, and -9.1, at weeks 12, 24 and 36 of the extension study, respectively. Similar findings were observed for IDSIQ sleepiness, alert/cognition and mood domain scores ($p<0.05$ for all) at weeks 12, 24, and 36 with the 50 mg dose of daridorexant.

In a phase 3 double-blind randomized controlled trial in Japan, 470 patients with insomnia disorder were enrolled, and 4 weeks of daridorexant treatment at the 50 mg dose significantly increased subjective total sleep time (+20.3 min, $p<0.001$) and decreased subjective latency to sleep onset (-10.7 min, $p<0.001$) compared to placebo at Week 4 (Uchimura et al., 2024). The 25 mg dose of daridorexant also significantly improved both endpoints versus placebo (+9.2 min, $p=0.042$; -7.2 min, $p=0.006$).

In a phase 3 open-label study of 154 Japanese people with insomnia disorder, daridorexant treatment (25 or 50 mg, nightly) for 1 year improved 'next-morning sleepiness' and 'sleep and daytime functioning' and these effects were maintained through to Week 52 (Uchimura et al., 2024). Because of the open-label study design, placebo effects cannot be ruled out.

In a real-world retrospective open-label study of 69 patients with chronic insomnia, daridorexant treatment (50 mg nightly) resulted in 58% of patients (and clinicians) rating their insomnia disorder as improved (measured by Clinical and Patient Global Impression-Improvement scores; CGI-Is and PGI-Is), 28% rating as unchanged, and 7.2% as worsened (Fernandes et al., 2024). Of these patients, 8 patients (33.3%) had absence of insomnia symptoms at the 30-day follow-up. Because of the retrospective and open-label study design, results are not able to establish causal relations.

In a network meta-analysis examining comparative efficacy across numerous approved medications for insomnia, daridorexant was recommended for managing sleep maintenance insomnia, while zolpidem was recommended for managing sleep-onset insomnia and sleep maintenance insomnia (with the caveat of daytime drowsiness effects)(Hasan et al., 2023). Objective total sleep time was increased with flurazepam by 48.9 min, lemborexant by 45.6 min, oxazepam by 45.1 min, tasimelteon by 37.1 min, zolpidem by 36.4 min, suvorexant by 34.1 min, daridorexant by 31.3 min, triazolam by 29.9 min, and quazepam by 29.7 min; all of these drugs were superior to placebo ($p<0.05$ for all).

Obstructive sleep apnea: IMPROVES SLEEP

In a double-blind randomized controlled crossover study of 28 people with mild or moderate obstructive sleep apnea, daridorexant treatment (50 mg per night) increased total sleep time by 39.6 minutes (p=0.007) after a single treatment and by 38.8 min (p=0.002) after 5 days of treatment, compared with placebo (Boof et al., 2021). Repeated-dose daridorexant (50 mg per night, for 5 days) did not impact the apnea/hypopnea index or peripheral oxygen saturation in these patients (Boof et al., 2022). There were also no treatment differences for the longest duration of apneas and hypopneas and lowest oxygen saturation.

Safety: Common adverse events include headache, somnolence, and fatigue. Daridorexant may have a better safety profile than other insomnia medications, but it may increase the risk of CNS depressant effects, daytime impairment, sleep paralysis, and others.

Types of evidence:

- 4 meta-analyses or systematic reviews
- 11 double-blind randomized controlled clinical trials
- Numerous posthoc analyses of phase 3 trials
- 2 open-label studies
- Numerous studies using the FDA Adverse Event Reporting System
- Numerous reviews

Common adverse events:

The most common adverse reactions with daridorexant are headache (up to 7%), somnolence (up to 6%), and fatigue (up to 6%) (drugs.com). Less common adverse events include dizziness (up to 3%), hypnagogic (occurring as you fall asleep) and hypnopompic (occurring as you wake up) hallucinations (0.6%), and sleep paralysis (up to 0.5%).

US prescribing information:

Warnings and precautions of daridorexant include central nervous system depressant effects, daytime impairment, worsening of depression/suicidal ideation, sleep paralysis, hypnagogic/hypnopompic hallucinations, cataplexy-like symptoms, and complex sleep behaviors (e.g., sleepwalking, sleep-driving, and engaging in activities while not fully awake)(Quviviqhcp.com).

Disease interactions:

Daridorexant is contraindicated in people with narcolepsy (drugs.com). People with a history of abuse or addiction to alcohol or other substances may be at increased risk of abuse of daridorexant. Daridorexant is a federally controlled substance (schedule IV) because it can be abused or lead to dependence at doses higher than the approved dose.

Daridorexant is a respiratory depressant and should be used with caution in people with impaired respiratory function. In a double-blind randomized controlled crossover study in people with moderate chronic obstructive pulmonary disease (COPD), daridorexant treatment (50 mg nightly) for 5 days did not impair night-time respiratory function, measured by peripheral oxygen saturation during sleep (Boof et al., 2021). The apnea-hypopnea index was slightly increased compared to placebo, but not to a clinically meaningful extent. Overall, daridorexant was well tolerated in people with COPD, with improved sleep parameters (increased total sleep time, increased sleep efficiency, and decreased 'wake time after sleep onset').

In a double-blind randomized controlled crossover trial in 28 people with mild or moderate obstructive sleep apnea, daridorexant treatment (50 mg nightly) for up to 5 days did not significantly affect apnea/hypopnea index or peripheral oxygen saturation, suggesting that daridorexant does not impair nighttime respiratory function in people with obstructive sleep apnea (Boof et al., 2021). Overall, the incidence of adverse events was similar with daridorexant compared to placebo.

Daridorexant is not recommended in people with severe hepatic dysfunction (drugs.com). The maximum dose in people with moderate hepatic dysfunction is 25 mg per night. Daridorexant can worsen depression and suicidal thoughts.

Drug interactions:

Daridorexant has 57 major drug interactions and 341 moderate drug interactions (drugs.com). Daridorexant must not be taken with other medications that are used to promote sleep. Daridorexant taken together with alcohol may increase side effects such as dizziness, drowsiness, confusion, difficulty concentrating, and impairment in thinking, judgment, and motor coordination. Daridorexant should not be taken with grapefruit, grapefruit juice, or any supplements that contain grapefruit extract, as grapefruit juice can increase blood levels of daridorexant, leading to greater risk of side effects.

Daridorexant is metabolized primarily by CYP3A4 (Preskorn, 2023; reviewed in Markham 2022). Coadministration of daridorexant (25 mg) with the moderate CYP3A4 inhibitor diltiazem increased daridorexant area under the curve (AUC) by 240%, and, based on pharmacokinetic modelling, coadministration with the strong CYP3A4 inhibitor, itraconazole, is expected to increase daridorexant AUC by > 400%. Coadministration of daridorexant with the moderate CYP3A4 inducer, efavirenz, decreased daridorexant AUC by ~35% and coadministration with the strong CYP3A4 inducer, rifampin, is expected to decrease daridorexant AUC by over 50%. Based on these fundings, the maximum recommended dose of daridorexant is 25 mg when used concomitantly with a moderate CYP3A4 inhibitor, and concomitant use of daridorexant and a strong CYP3A4 inhibitor, or moderate or strong CYP3A4 inducer is not recommended.

Daridorexant at a dose of 50 mg can be coadministered with famotidine (histamine 2 receptor inhibitor) without dosage adjustment (reviewed in Markham 2022). Coadministration of daridorexant at a dose of 50 mg with citalopram (SSRI) was not associated with clinically relevant changes in pharmacokinetic parameters. Coadministration of daridorexant with rosuvastatin (statin) did not affect the pharmacokinetics of rosuvastatin.

Clinical trial findings:

Numerous randomized controlled trials as well as meta-analyses of randomized controlled trials have evaluated the safety of daridorexant treatment. Almost all studies have been carried out in people with insomnia.

In a 2023 meta-analysis of 4 randomized controlled trials including a total of 2,227 people with insomnia disorder, daridorexant treatment (25 or 50 mg nightly) was well tolerated, with the most common adverse events being nasopharyngitis, fatigue, and headache (Jiang et al., 2023). Subgroup analyses showed that there were no differences in safety between people ≥65 years and under 65.

In a 2023 meta-analysis of 7 randomized controlled trials including a total of 2,425 people with insomnia, daridorexant treatment for up to 3 months resulted in increased risk for somnolence (RR=1.19, p=0.005) and fatigue (RR=2.01; p=0.007), but no differences compared to placebo in experiencing headache, dizziness, nausea, and nasopharyngitis (Albadrani et al., 2023).

In a 2023 meta-analysis of 4 randomized controlled trials including a total of 2,768 people with insomnia (1,962 people randomized to daridorexant), treatment-emergent adverse events with daridorexant

were significantly higher in prevalence than placebo (RR=1.23; p=0.008)(Dutta et al., 2023). However, at the 25 mg (RR=1.12) and 50 mg dose (RR=1.25), there was no significant risk of treatment-emergent adverse events compared to placebo. Daridorexant treatment did not significantly increase the risk of serious adverse events compared to placebo.

In two phase 3 double-blind randomized controlled trials that enrolled a total of 1854 adults with insomnia, daridorexant treatment resulted in an overall incidence of adverse events that was comparable to placebo (Mignot et al., 2022). The prevalence of adverse events was consistent across people ≥65 years and under 65. Nasopharyngitis and headache were the most common adverse events in all groups. One death caused by cardiac arrest occurred in the daridorexant 25 mg dose group (with pre-existing risk factors), and it was not deemed to be treatment-related. Events associated with excessive daytime sleepiness were reported in less than 1% of participants overall (1/308 [<1%] with the 50 mg dose, 2/310 [1%] with the 25 mg dose, and 1/309 [<1%] with placebo in Study 1; 4/308 [1%] with the 25 mg dose, 1/306 [<1%] with the 10 mg dose, and 1/306 [<1%] with placebo in Study 2). One participant in the daridorexant 50 mg group and 1 in the 25 mg group in Study 1, and 2 participants in the daridorexant 25 mg group in Study 2 reported sleep paralysis, and 1 participant in the daridorexant 25 mg group in Study 1 and 3 in the daridorexant 25 mg group in Study 2 reported hallucinations. There were no events of other complex sleep behaviors (e.g., cataplexy). Suicidal ideation was reported in 2 participants (1 in each daridorexant dose group) in Study 2, and in both cases, confounding factors were present at baseline (both patients had pre-existing paranoid schizophrenia or depression) and the independent safety board adjudicated both adverse events as potentially related to trial treatment. No adverse events suggested drug misuse and there were no withdrawal symptoms observed during the placebo run-out period. During the placebo run-out period, 'wake time after sleep onset' and 'latency to persistent sleep' were numerically lower, and self-reported total sleep time was higher than baseline values, indicating an absence of rebound insomnia.

In a secondary analysis of the phase 3 trial (Study 1), efficacy of daridorexant was compared between older patients (≥65 years) and younger patients (under 65 years)(Fietze et al., 2022). The overall incidence of adverse events was comparable between the two age groups, and there were fewer falls on daridorexant compared to placebo. Daridorexant improved morning sleepiness (Visual Analog Scale) in both younger and older patients; daridorexant at the 50 mg dose increased the mean morning sleepiness score by 15.9 in older adults and by 14.9 in younger adults from baseline to month 3. In older adults, there was 1 case of sleep paralysis, and no cases of narcolepsy, cataplexy, or other complex sleep behaviors. Older adults are not at an increased risk of adverse events or next-morning residual effects at the 50 mg dose, and therefore the dose does not need to be decreased for older patients. The clinical

benefit of daridorexant was greatest at the 50 mg dose in older patients, without an increase in adverse events.

In a Japanese phase 3 double-blind randomized controlled trial of 470 patients with insomnia disorder, daridorexant treatment (25 mg or 50 mg, nightly) for 4 weeks had adverse event incidences that were similar across groups (22 % with the 50 mg dose; 18% with the 25 mg dose; 23% with placebo) (Uchimura et al., 2024). Somnolence was the most common adverse event and it increased with increasing dose (6.8% with the 50 mg dose, 3.7% with the 25 mg dose, 1.8% with placebo). However, daridorexant treatment did not increase next-morning sleepiness. No rebound or withdrawal-related symptoms were observed after treatment discontinuation. Only one independent safety board-adjudicated adverse event of special interest was reported; sleep paralysis with the 50 mg dose was experienced by a female patient aged 57 years old with no comorbidities. The adverse event was mild and non-serious, with resolution on Day 2 of treatment.

In a double-blind randomized controlled crossover study in 72 people with recreational sedative drug users, a single oral morning dose of daridorexant at the approved dose (50 mg) had a significantly lower drug-liking visual analog scale compared to a supratherapeutic dose of suvorexant (50 mg) or zolpidem (30 mg), but it was higher than placebo (Ufer et al., 2022). However, at higher doses of daridorexant (100 mg and 150 mg), the drug-liking visual analog scale was similar to the supratherapeutic doses of suvorexant and zolpidem. Given this study was carried out in recreational sedative drug users, it is not clear how translatable these findings are to patients with insomnia, where there was a lack of abuse signal in the large phase 3 trials. All daridorexant doses (50, 100, and 150 mg) and suvorexant and zolpidem showed dose-related sedative effects that were differentiated from placebo. Daridorexant treatment at the 50 mg dose showed significantly less cognitive impairment compared to zolpidem and suvorexant (measured by reaction time, response latency, and total errors). Because the drugs were given in the morning, and cognitive assessments were carried out during the time frame when the drugs are promoting sleep induction and maintenance, the negative effects on cognitive function are expected. These findings do not translate to cognitive impairment in people who take daridorexant before bedtime, with the expectation that they would be sleeping for the following ~7 hours. Accordingly, somnolence was the most reported adverse event with dose-related incidence of 44.8% (50 mg), 59.4% (100 mg), and 80.6% (150 mg) following administration of daridorexant as compared to 68.7% and 53.6% after administration of suvorexant and zolpidem, respectively.

In a double-blind randomized controlled crossover study of 36 healthy people, single doses of daridorexant (50 mg or 200 mg) at bedtime did not impair cardiac repolarization as measured by the

absence of relevant QT (QTcF) prolongation at therapeutic (50 mg) and supratherapeutic (200 mg) doses (Schilling et al., 2021).

Long-term safety:

A few clinical trials have evaluated the long-term safety of daridorexant up to 1 year of treatment, and these studies did not observe new safety signals. In a long-term follow-up of the two phase 3 trials, 550 patients with insomnia completed a total of 52 weeks of intervention (daridorexant 10/25/50 mg nightly or placebo for 12 weeks, followed by a 40-week double-blind controlled extension, then a 7-day placebo run-out)(Kunz et al., 2023). The overall incidence of treatment-emergent adverse events was similar across groups (35-40%). Daridorexant did not induce next-morning sleepiness and no withdrawal-related symptoms or rebound were observed after treatment discontinuation. Most treatment-emergent adverse events occurring during the 40-week double-blind extension period were mild or moderate in severity (91.2%). The most commonly reported treatment-emergent adverse events in all groups was nasopharyngitis. Treatment-emergent adverse events leading to discontinuation of participation were reported only for single patients in any given group. Two serious treatment-emergent adverse events assessed as related to study medication by the investigator were orthostatic intolerance (daridorexant at the 25 mg dose) and depression/suicidal ideation (placebo). Two deaths, both cardiovascular related, were reported during the study (1 each with the 10 mg and 25 mg dose of daridorexant) and assessed by the investigator as not related to study treatment. There were 3 independent safety board-adjudicated adverse events of special interest. One non-serious event related to excessive daytime sleepiness (fell asleep or napped during daytime less than or once per week) was reported with the 25 mg dose of daridorexant, with an onset on day 44 and resolved on day 93. The patient discontinued the study on day 98. A second non-serious treatment-emergent adverse event of hallucinations/sleep paralysis was reported in a patient taking the 50 mg dose of daridorexant; this patient experienced mild events of abnormal dreams (no impression of fear or being in a nightmare) on days 1, 2 and 4 of the extension study, awaking 1-1.5 hour after taking the study drug. The adverse event was resolved thereafter. A third serious adverse event of special interest was suicidal ideation, and it was reported in the placebo group. No complex sleep behavior or cataplexy was reported in any patient. Accidental overdose (unintentionally took or were uncertain of whether they had taken an extra tablet) was reported in 15 patients receiving daridorexant (2.8% with the 10 mg dose, 1.1% with the 25 mg dose, 2.9% with the 50 mg dose; 3.2% in the ex-placebo/daridorexant 25 mg group). All cases were asymptomatic, mild, and non-serious. There were no treatment-emergent adverse events denoting euphoria. Fall was reported in 14 patients across treatment groups (1.4% with the 10 mg dose, 2.2% with the 25 mg dose, 2.2% with the 50 mg dose; 0.8% in the ex-placebo/daridorexant 25 mg group, and

1.6% with placebo). None of the falls were serious and, in all cases, external contributing factors (e.g., stumbling, slippery floor) were reported. Participants taking daridorexant did not show excessive daytime sleepiness compared to those taking placebo. There was no evidence of any withdrawal-related symptoms upon cessation of daridorexant (measured by BWSQ, benzodiazepine withdrawal symptom questionnaire). Changes from the last assessment with daridorexant/placebo to the placebo run-out period were minor with no relevant differences between daridorexant and placebo groups, and no dose dependency observed. During the placebo run-out period, mean self-reported total sleep time was numerically higher than baseline, suggesting no rebound insomnia after daridorexant discontinuation. There were no clinically significant findings related to hematology or clinical chemistry parameters, vital signs, body weight, or electrocardiographic parameters.

In a phase 3 open-label study of 154 Japanese people with insomnia disorder, daridorexant treatment (25 or 50 mg, nightly) for one year resulted in treatment-emergent adverse events at incidences of 74% and 58% with 50 mg and 25 mg doses, respectively, with most adverse events being mild or moderate in severity (Uchimura et al., 2024). There were no serious treatment-emergent adverse events considered to be related to daridorexant (osteoarthritis, Guillain-Barre syndrome, idiopathic pulmonary fibrosis, Dupuytren's contracture, unstable angina, cholangitis, COVID-19, subdural hematoma, and aortic dissection). Common treatment-emergent adverse events included somnolence, headache, and malaise. Malaise was reported in 9 patients (8.8%) taking the 50 mg dose and none in the 25 mg dose group. Five independent safety board-adjudicated adverse events were reported: excessive daytime sleepiness (n=1 with 25 mg; n=2 with 50 mg), sleep paralysis (n=1 with 50 mg) and nightmare (n=1 with 25 mg). The rate of discontinuation (21%) was similar in both 25 mg and 50 mg doses of daridorexant. There were no clinically significant findings for any changes in hematology or clinical chemistry parameters, vital signs, body weight, or electrocardiographic parameters.

Cognitive outcomes:

In phase 1 and 2 studies in 71 insomnia patients in Japan, the effects of daridorexant treatment (10, 25, or 50 mg) on cognitive function were evaluated (Uchiyama et al., 2024). Scores for attention, perception speed, motion speed, visual scanning, and memory (measured by DSST), next-day alertness (measured by KSS-J), and performance on work, social life, and home responsibilities (measured by SDS) were not significantly affected by daridorexant on the morning after taking the drug and after 14 days of treatment; there were no dose-dependent changes in any of these measures.

In a randomized controlled crossover trial of 60 healthy men and women (50-79 years old), daridorexant treatment increased the standard deviation of the lateral position (SDLP; measure of "swerving") on the simulated driving performance by 2.19 cm and 4.43 cm for the 50 mg and 100 mg dose, respectively, on day 2, but by day 5, both daridorexant doses resulted in significantly below the prespecified threshold of impairment (2.6 cm) and statistically not different from placebo (Muehlan et al., 2022). In contrast, zopiclone showed significantly increased SDLP on both days 2 and 5. Daridorexant treatment showed a lower self-rated driving quality and higher effort compared to placebo on day 2 but not on day 5. Because this study was carried out in healthy sleepers who likely have an orexin system that is not hyperactive, it is possible that greater impairment was observed with daridorexant than what might be expected in people with insomnia.

In a 2024 network meta-analysis of 22 randomized controlled crossover trials testing various insomnia medications, ramelteon 8 mg, daridorexant 100 mg (higher than the approved dose), zolpidem 10 mg at bedtime, zolpidem 10 mg and 20 mg at middle-of-the-night, mirtazapine 15-30 mg, and triazolam 0.5 mg were associated with significantly worse simulated driving performance compared to placebo, measured by SDLP (Fornaro et al., 2024). At the approved dose of 50 mg of daridorexant, simulated driving performance was comparable to placebo. Repeated administration of daridorexant (50-100 mg) for up to 15 days caused fewer residual effects, with simulated driving performance paralleling placebo.

Findings from the FDA Adverse Event Reporting System (FAERS):

In a 2024 study using the FAERS database, 1,318 adverse events related to daridorexant were analyzed (Wang et al., 2024). Signal mining identified adverse events related to daridorexant, including sleep-related psychiatric symptoms (nightmare, abnormal dreams, sleep terror, etc.), emotional and perceptual abnormalities (hallucination, depression, agitation), physiological and behavioral responses (palpitations, dry mouth, energy increased, etc.), suicide risk (suicidal ideation, intentional overdose), and other adverse events (tachyphrenia--racing thoughts, sleep-related eating disorder, and hypersensitivity). 'Preferred terms' identified through signal mining and ranked by signal strength and frequency of occurrence include: 'drug ineffective' (324 cases, 24.58%), 'nightmare' (205 cases, 15.56%), 'insomnia' (156 cases, 11.84%), 'product availability issue' (103 cases, 7.82%), and 'abnormal dreams' (94 cases, 7.13%). Information collected through FAERS may be subject to reporting biases, and the study cannot account for interactions between daridorexant and other medications. Thus, these findings need further verification in broader datasets and long-term studies.

In another 2024 study using the FAERS database, the reporting odds ratios (RORs) of daridorexant were compared to RORs of all other drugs and RORs of other dual orexin receptor antagonists (Cicala et al., 2024). Daridorexant was associated with higher RORs for nightmares, depression, and hangover compared to all other drugs as well as compared to other dual orexin receptor antagonists.

In a 2024 study using the FAERS database, 11,857 adverse reactions related to dual orexin receptor antagonists were evaluated (Jiang et al., 2024). Of the 'preferred terminology' signals from the three drugs (daridorexant, suvorexant, and lemborexant), 'sleep paralysis' ranked first. 'Brain fog' was stronger in people taking daridorexant, but was not detected for suvorexant or lemborexant. As in the above studies, the recorded adverse events were derived from consumers and there may be reporting biases, including the impact of the disease itself and concomitant medications.

Pharmacokinetics:

Daridorexant has a binding affinity for OX1 and OX2 at 0.47 nM and 0.93 nM, respectively (Preskorn, 2022). Half-life of daridorexant is ~8 hours, which is shorter than the two other approved dual orexin receptor antagonists (17-19 hours for lemborexant and 12-15 hours for suvorexant). Tmax is 1-2 hours. A high fat, high calorie meal delays Tmax by 1.3 hours.

Pregnancy/breastfeeding:

In an open-label study of 10 healthy lactating women, a single dose of daridorexant (50 mg) in the morning resulted in measurable but trace quantities of daridorexant and its major metabolites in breast milk (Kaufmann et al., 2024). The cumulative total amount of daridorexant excreted over 72 hours was 0.010 mg, which corresponds to 0.02% of the dose given, and 45- to 50-fold lower compared to plasma. This corresponds to a mean daily infant dose of 0.009 mg/day and a relative infant dose of less than 0.22% over 24 hours. At this time, potential effects on the breastfed infant are unknown, and a risk of somnolence or other depressant effects cannot be excluded. Continuous postmarketing data will inform the safety and tolerability in infants breastfed by lactating women taking daridorexant.

Sources and dosing:

Daridorexant, marketed as Quviviq by Idorsia Pharmaceuticals, Ltd., is approved for the treatment of insomnia.

The recommended dose for adults with insomnia is 25 to 50 mg, once per night, orally. Daridorexant should be taken within 30 minutes of going to bed, and with at least 7 hours remaining prior to waking (drugs.com). The maximum dose is 50 mg per night.

Based on Drugs.com, daridorexant has an average rating of 5.0 out of 10 from a total of 151 reviews; 38% of reviewers reported a positive experience and 48% reported a negative experience (23% of reviewers gave it a rating of 10, 8% gave a 9, and 38% gave a 1). Negative reviews were related to lack of efficacy and the high cost.

Research underway:

Based on ClinicalTrials.gov, there are 7 ongoing studies investigating daridorexant. Four of these studies are testing daridorexant in patients with insomnia. One of these studies is investigating pregnancy, neonatal, and infant outcomes in women exposed to daridorexant during pregnancy (NCT06498128).

A phase IV randomized crossover clinical trial (DARIDOR-ALZ) is evaluating the efficacy and safety of daridorexant (50 mg per night) in 62 people with mild cognitive impairment or mild-to-moderate Alzheimer's patients with insomnia complaints (NCT05924425). The primary outcome is change in total sleep time. This study is scheduled to be completed in March 2027.

A phase 2 clinical trial is testing whether daridorexant treatment (50 mg per night) prevents delirium in 12 patients receiving heart surgery (NCT06630390). The primary outcome is delirium in the first 3 days after surgery. This study is scheduled to be completed in March 2025.

Search terms:

Pubmed, Google: daridorexant

Websites visited for daridorexant:

- Clinicaltrials.gov
- NIH RePORTER (0)
- DrugAge (0)
- Geroprotectors (0)
- Drugs.com

- PubChem
- DrugBank.ca
- Pharmapro.com (0)

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