Daridorexant (QUVIVIQ)
National Drug Monograph
June 2022

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Daridorexant is an orexin receptor antagonist

Indication(s) Under Review in This Document

- Daridorexant is indicated for the treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance

Dosage Form(s) Under Review

- Tablets: 25 mg, 50 mg

Clinical Evidence Summary

Efficacy Considerations

- The efficacy of daridorexant, supporting its FDA approval, was evaluated in two multicenter, randomized, double-blind, placebo-controlled, phase 3 trials, (Study 1, NCT03545191) and (Study 2, NCT03575104) in adults with insomnia disorder.
- Patients were randomly assigned to receive daridorexant 50 mg, 25 mg, or placebo (Study 1) or daridorexant 25 mg, 10 mg, or placebo (Study 2) every evening for 3 months.
- The primary endpoints were change from baseline in wake time after sleep onset (WASO) and latency to persistent sleep (LPS), measured by polysomnography, at months 1 and 3. LPS is a measure of sleep induction and WASO is a measure of sleep maintenance. What constitutes a clinically meaningful change in LPS and WASO has been suggested by the American Academy of Sleep Medicine (AASM) expert consensus.[7] They suggest a 20 and 10 minutes (lowering) difference from placebo in WASO and LPS respectively.
- The secondary endpoints were change from baseline in self-reported total sleep time (sTST) and the sleepiness domain score of the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ), using eDiary, at months 1 and 3.
- In study 1, WASO and LPS were significantly reduced among participants in the daridorexant 25 mg and 50 mg groups compared with participants in the placebo group at month 1 and month 3

(Table 1). Applying the AASM consensus criteria, there is evidence of clinically meaningful efficacy only for the 50-mg dose.

- Compared with placebo, participants in the daridorexant 25 mg and 50 mg groups had significantly improved sTST at month 1 and month 3. However, only the 50 mg group displayed improvements in the IDSIQ sleepiness domain scores at month 1 and month 3 (Table 2).
- In study 2, WASO and LPS was significantly reduced among participants in the daridorexant 25 mg group compared with participants in the placebo group at month 1 and month 3 (Table 1).
- Compared with the placebo group, participants in the daridorexant 25 mg group (Study 2) had significant improvement in sTST at month 1 and month 3 but not in IDSIQ sleepiness domain scores at month 1 (Table 2).
- Compared with the placebo group, no significant differences were observed among participants in the daridorexant 10 mg group for WASO, LPS, or IDSIQ at month 1 or month 3.
- Nasopharyngitis, headache, and somnolence or fatigue were the most common adverse events in all groups (Table 3).

Table 1. Primary Efficacy Endpoints.[5]

	Study 1			Study 2		
	Dari 50mg (N=310)	**Dari 25mg (N=310)**	**Placebo (N=310)**	**Dari 25mg (N=309)**	**Dari 10mg (N=307)**	**Placebo (N=308)**
WASO, min, BL Mean (SD)	95.5 (37.8)	97.9 (38.8)	102.5 (40.8)	106.0 (49.1)	104.6 (46.2)	108.1 (48.7)
WASO, min, 1 month Δ BL (95% CI)	- 29.0 (-32.7, -25.3)	- 18.4 (-22.1, - 14.7)	- 6.2 (-9.9, –2.5)	-24.2 (-28.5, -19.9)	-15.3 (-19.5, -11.1)	-12.6 (-16.3, -8.3)
Difference vs. Placebo (95% CI)	-22.8 (-28.0, -17.6)	-12.2 (-17.4, -7.0)	-	-11.6 (-17.6, -5.6)	-2.7 (-8.7, 3.2)	-
p-value (vs. Placebo)	P<0.0001	P<0.0001	-	P=0.0001	P=0.37	-
WASO, min, 3 month Δ BL (95% CI)	-29.4 (-33.4, -25.4)	-23.0 (-27, -19)	-11.1 (-15.1, -7.1)	-24.3 (-29.0, -19.5)	-16.0 (-20.7, -11.2)	-14.0 (-18.8, -9.2)
Difference vs. Placebo (95% CI)	-18.3 (-23.9, -12.7)	-11.9 (-17.5, -6.2)	-	-10.3 (-17.0, -3.5)	-2.0 (-8.7, 4.8)	-
p-value (vs. Placebo)	P<0.0001	P<0.0001	-	P=0.003	P=0.57	-
LPS, min, BL Mean (SD)	63.6 (37.4)	67.3 (38.6)	66.5 (39.8)	68.9 (40.5)	67.4 (41.7)	71.8 (46.1)
LPS, min, 1 month Δ BL (95% CI)	-31.2 (-34.5, -27.9)	-28.2 (-31.5, -24.8)	-19.9 (-23.2, -16.5)	-26.5 (-30.6, -22.3)	-22.6 (-26.7, -18.5)	-20.0 (-24.1, -15.9)
Difference vs. Placebo (95% CI)	-11.4 (-16.0, -6.7)	-8.3 (-13.0, -3.6)	-	-6.5 (-12.3, -0.6)	-2.6 (-8.4, 3.2)	-
p-value (vs. Placebo)	P<0.0001	P=0.0005	-	P=0.03	P=0.38	-
LPS, min, 3 month Δ BL (95% CI)	-34.8 (-38.1, -31.5)	-30.7 (-34.0, -27.4)	-23.1 (-26.5, -19.8)	-28.9 (-33.4, -24.4)	-23.1 (-27.6, -18.6)	-19.9 (-24.4, -15.4)
Difference vs. Placebo (95% CI)	-11.7 (-16.3, -7.0)	-7.6 (-12.3, -2.9)	-	-9.0 (-15.3, -2.7)	-3.2 (-9.5, 3.1)	-
p-value (vs. Placebo)	P<0.0001	P=0.0015	-	P=0.0053	P=0.32	-

BL: baseline; SD: standard deviation; CI: confidence interval; LPS: latency to persistent sleep; WASO: wake time after sleep onset; Dari, daridorexant; min, minute.

Table 2. Secondary Endpoints.[5]

	Study 1			Study 2		
	Dari 50mg (N=310)	**Dari 25mg (N=310)**	**Placebo (N=310)**	**Dari 25mg (N=309)**	**Dari 10mg (N=307)**	**Placebo (N=308)**
sTST, min, BL Mean (SD)	328.3 (50.2)	309.8 (60.1)	315.9 (53.1)	308.5 (52.8)	308.4 (51.4)	307.6 (51.5)
sTST, @ month 1, min, Δ BL (95% CI)	43.6 (38.2, 49.1)	34.2 (28.7, 39.6)	21.6 (16.1, 27.0)	43.8 (38.1, 49.4)	41.0 (35.4, 46.6)	27.6 (22.0, 33.3)
Difference vs. Placebo (95% CI)	22.1 (14.4, 29.7)	12.6 (5.0, 20.3)	-	16.1 (8.2, 24.0)	13.4 (5.5, 21.2)	-
p-value (vs. Placebo)	P<0.0001	P=0.0013	-	P<0.0001	P=0.0009	-
sTST, @ month 3, min, Δ BL (95% CI)	57.7 (51.2, 64.2)	47.8 (41.3, 54.3)	37.9 (31.4, 44.4)	56.2 (49.8, 62.5)	50.7 (44.4, 57.0)	37.1 (30.8, 43.5)
Difference vs. Placebo (95% CI)	19.8 (10.6, 28.9)	9.9 (0.8, 19.1)	-	19.1 (10.1, 28.0)	13.6 (4.7, 22.5)	-
p-value (vs. Placebo)	P<0.0001	P=0.033	-	P<0.0001	P=0.0028	-
IDSIQ score, BL Mean (SD)	22.5 (7.2)	22.1 (6.9)	22.3 (6.9)	22.2 (6.2)	22.7 (6.3)	22.6 (5.8)
IDSIQ @ month 1, Δ BL (95% CI)	-3.8 (-4.3, -3.2)	-2.8 (-3.3, -2.2)	-2.0 (-2.6, -1.5)	-3.5 (-4.1, -2.9)	-3.2 (-3.8, -2.6)	-2.8 (-3.3, -2.2)
Difference vs. Placebo (95% CI)	-1.8 (-2.5, -1.0)	-0.8 (-1.5, 0.01)	-	-0.8 (-1.6, 0.1	-0.4 (-1.3, 0.4)	-
p-value (vs. Placebo)	P<0.0001	P=0.055	-	P=0.073	P=0.30	-
IDSIQ @ month 3, Δ BL (95% CI)	-5.7 (-6.4, -5.0)	-4.8 (-5.5, -4.1)	-3.8 (-4.5, -3.1)	-5.3 (-6.0, -4.6)	-4.8 (-5.4, -4.1)	-4.0 (-4.7, -3.3)
Difference vs. Placebo (95% CI)	-1.9 (-2.9, -0.9)	-1.0 (-2.0, 0.01)	-	-1.3 (-2.2, -0.3)	-0.7 (-1.7, 0.2)	-
p-value (vs. Placebo)	P=0.0002	P=0.053	-	P=0.012	P=0.14	-

BL: baseline; SD: standard deviation; CI: confidence interval; Dari, daridorexant; min, minute; IDSIQ=Insomnia Daytime Symptoms and Impacts Questionnaire, sleepiness domain score; sTST, self-reported total sleep time.

Safety Considerations

Table 3. Adverse Events, ≥2% in any group[5]

	Study 1			Study 2		
	Dari 50mg (N=308)	Dari 25mg (N=310)	Placebo (N=309)	Dari 25mg (N=308)	Dari 10mg (N=306)	Placebo (N=306)
Nasopharyngitis	20 (6%)	21 (7%)	20 (6%)	13 (4%)	32 (10%)	16 (5%)
Headache	19 (6%)	16 (5%)	12 (4%)	15 (5%)	12 (4%)	11 (4%)
Accidental overdose	8 (3%)	4 (1%)	5 (2%)	4 (1%)	4 (1%)	1 (<1%)
Fatigue or somnolence	12 (4%)	18 (6%)	8 (3%)	21 (7%)	13 (4%)	6 (2%)
Dizziness	7 (2%)	6 (2%)	2 (1%)	6 (2%)	4 (1%)	4 (1%)
Nausea	7 (2%)	1 (<1%)	3 (1%)	2 (1%)	3 (1%)	3 (1%)
Fall	1 (<1%)	1 (<1%)	8 (3%)	3 (1%)	4 (1%)	3 (1%)
Upper respiratory tract infection	1 (<1%)	1 (<1%)	3 (1%)	3 (1%)	5 (2%)	6 (2%)

Dari, daridorexant

Contraindications [1]

- Narcolepsy

Other Warnings / Precautions:[1]

- CNS-Depressant effects and daytime impairment
- Worsening of depression/suicidal ideation
- Sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms
- Complex sleep behaviors
- Patients with compromised respiratory function
- Need to evaluate for co-morbid diagnoses

Drug Interactions [1]

- Co-administration with strong CYP3A inhibitors
- Co-administration with moderate or strong CYP3A4 inducers

Other Therapeutic Options

Table 4.

Drug	Formulary status	Clinical Guidance/ Indication	Other Considerations
Daridorexant	NF with CFU	treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance	Contraindicated in narcolepsy Once daily administration Avoid with strong CYP3A4 inhibitors and moderate or strong CYP3A4 inducers Not recommended in severe hepatic impairment (Child-Pugh C)
Lemborexant	NF with CFU	treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance	Contraindicated in narcolepsy Once daily administration Avoid with strong or moderate CYP3A4 inhibitors and strong or moderate CYP3A4 inducers Not recommended in severe hepatic impairment
Suvorexant	NF with CFU	treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance	Contraindicated in narcolepsy Once daily administration Not recommended with strong CYP3A4 inhibitors Not recommended in severe hepatic impairment

Projected Place in Therapy

- Insomnia is the most common sleep disorder, affecting more than 25 million adults in the US.[13] The National Institutes of Health estimates roughly 30% of the general population complains of sleep disruption, and approximately 10% have the associated symptoms of daytime functional impairment.[8] The prevalence of chronic insomnia disorder is estimated to be between 6% and 10%, while the prevalence of insomnia symptoms has been reported to be as high as 41% in Service Members deployed to combat and 25% in noncombatants.[9-11]
- Cognitive Behavioral Therapy for Insomnia (CBT-I) is considered the most effective treatment for insomnia.
- The results from Study 1 and Study 2 showed that the primary efficacy measures, WASO and LPS, were significantly improved among participants in the daridorexant 25 mg and 50 mg groups compared with participants in the placebo group at month 1 and month 3. However, applying AASM consensus criteria, there is evidence of clinically meaningful efficacy only for the 50mg dose.
- Compared with the placebo group, no significant differences were observed among participants in the daridorexant 10 mg group for WASO or LPS at month 1 or month 3.
- The VA/DoD CPG for the management of chronic insomnia disorder and obstructive sleep apnea[12] states that "there is insufficient evidence to recommend for or against the use of

suvorexant for the treatment of chronic insomnia disorder." The use of lemborexant and daridorexant were not addressed in the Guideline.

- The orexin receptor antagonists (suvorexant, lemborexant, daridorexant) have the same indication (treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance), warning/precautions, and are Schedule IV controlled substances. There are differences in drugs that should be avoided among the agents, from a drug-drug interaction standpoint. However, there are no head-to-head clinical trials among these agents. Daridorexant, a third orexin antagonist, represents another treatment option for the management of insomnia.

References

1. QUVIVIQ (daridorexant) [prescribing information]. Idorsia Pharmaceuticals. Radnor, PA. 2022.
2. BELSOMRA (suvorexant) [prescribing information]. Merck & Co. Whitehouse Station, NJ. 2021.
3. DAYVIGO (lemborexant) [prescribing information]. Eisai Inc. Nutley, NJ. 2021.
4. NDA 214985. NDA approval letter. Department of Health and Human Services. Food and Drug Administration, Silver Spring, MD 20993. January 7, 2022.
5. Mignot E, Mayleben D, Fietze I et al. Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials. Lancet Neurol 2022;21:125-139.
6. FDA Integrated Review. Application number 214985Orig1s000. Center for Drug Evaluation and Research. September 22, 2021.
7. Sateia MJ, Buysse DJ, Krystal AD et al. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2017;13:307-349.
8. National Institutes of Health. National Institutes of Health state of the science conference statement on manifestations and management of chronic insomnia in adults, June 13-15, 2005. Sleep 2005;28:1049-1057.
9. Ohayon MM. Epidemiology of insomnia: What we know and what we still need to learn. Sleep Med Rev Apr 2002;6:97-111.
10. Morin CM, Benca R. Chronic insomnia. Lancet 2012;379:1129-1141.
11. Taylor DJ, Pruiksma KE, Hale WJ, et al. Prevalence, correlates, and predictors of insomnia in the US Army prior to deployment. Sleep 2016;39:1795-1806.
12. VA/DoD CPG for the management of chronic insomnia disorder and obstructive sleep apnea. Oct 2019.
13. Bhaskar S, Hemavathy D, Prasad S. Prevalence of chronic insomnia in adult patients and its correlation with medical comorbidities. J Family Med Prim Care 2016;5:780-784.

Prepared May 2022. Contact person: Matthew A. Fuller, Pharm.D, BCPP, National PBM Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services (12PBM)