**Daridorexant (Quviviq®)**
**FDA approved January 2022 (Idorsia Pharmaceuticals Inc)**
**Schedule IV controlled substance**

**Indications:** Insomnia characterized by difficulties with sleep onset and/or sleep maintenance

**Mechanism of action**

- Daridorexant is a dual orexin receptor antagonist (DORA) that blocks the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R, presumed to suppress wake drive

| | |
|---|---|
| **Dosage** | 25 to 50 mg PO qhs within 30 minutes of going to bed, with at least 7 hours remaining before planned time of awakening |
| **Administration** | • Administer without food prior to bedtime<br>• Onset of action may be delayed with food, do not administer with (or soon after a meal) |
| **Hepatic impairment** | • Moderate (Child-Pugh 7 - 9): 25 mg no more than once per night<br>• Severe (Child-Pugh ≥ 10): Avoid use |
| **Renal Impairment** | No dosage adjustment is recommended |
| **Geriatric Patients** | No dosage adjustment needed |
| **Pts with compromised respiratory function** | Inadequate data supporting use in obstructive sleep apnea and/or COPD |
| **How Supplied** | 25 & 50 mg tabs |

**Adverse Reactions**
Most frequently reported AEs (≥5% & at an incidence ≥ placebo): Headache & somnolence or fatigue

**Table 1 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 |

**DORAs adverse effects comparison**

| | Lemborexant (Dayvigo) | Daridorexant (Quviviq) | Suvorexant (Belsomra) |
|---|---|---|---|
| **Common (> 10%)** | Drowsiness<br>Fatigue | | Drowsiness |
| **More Frequent (4%-10%)** | Headache | Drowsiness<br>Fatigue<br>Headache | Headache |
| **Less Frequent** | Abnormal Dreams | Dizziness | Abnormal Dreams, cough, diarrhea, |

| | | | |
|---|---|---|---|
| **(1%-4%)** | Nightmares<br>Sleep Paralysis | Nausea | dizziness, upper respiratory tract infection, xerostomia |
| **Rare (< 1%)** | Complex Sleep-Related Disorder, hypnogenic, hallucinations | Hallucination, hypnogenic, hallucinations, sleep paralysis | Abnormal dreams, cough, diarrhea, dizziness, upper respiratory tract infection, xerostomia |
| **Unknown incidence** | Cataplexy, CNS depression, palpitations | Daytime Sedation | Abnormal Behavior, amnesia, anxiety, behavioral changes, cataplexy, drug abuse, exacerbation of depression, hallucination, increased serum cholesterol, lower extremity weakness, mental health disorders, sleep driving, suicidal ideation, suicidal tendencies, suicide, worsening of cognitive function |

**Warnings & Precautions**

| | |
|---|---|
| CNS depressant effects & daytime impairment | Risk increases with dose or if used with other CNS depressants (eg, benzos, opioids, TCAs, alcohol). Use with other drugs to treat insomnia is not recommended |
| Sleep paralysis, hypnogogic/hypnopompic hallucinations, and cataplexy-like symptoms | Risk of sleep paralysis (inability to move or speak for up to several minutes during sleep-wake transitions), hypnagogic/hypnopompic hallucinations, and mild cataplexy-like symptoms can occur. Cataplexy symptoms may include leg weakness lasting from seconds to a few minutes |
| Complex sleep behaviors | Sleep related activities such as “sleep driving” & other behaviors (eg, preparing and eating food, making phone calls, or having sex) have been reported with the use of orexin receptor antagonists |
| Compromised respiratory function | Effect on respiratory function should be considered |
| Worsening of depression/suicidal ideation | Use with caution in patients with depression. As with other hypnotics daridorexant should be administered with caution in patients displaying symptoms of depression. Consider prescribing the lowest number of tablets to avoid intentional overdose |
| Need to evaluate for co-morbid diagnoses | Reevaluate if insomnia persists after 7 to 10 days of treatment |

**Contraindication:** Narcolepsy

**Interactions**

| Concomitant Medication | Effect |
|---|---|
| **Strong CYP3A inhibitors**<br>Strong CYP3A inhibitors: itraconazole, clarithromycin | Avoid concomitant use<br>(increased r/o AEs) |
| **Moderate CYP3A inhibitors**<br>Moderate CYP3A inhibitors: fluconazole, verapamil | Recommended dose 25 mg qhs |
| **Strong or Moderate CYP3A Inducers**<br>Strong CYP3A inducers: rifampin, carbamazepine, St. John’s wort.<br>Moderate CYP3A inducers: bosentan, efavirenz, etravirine, modafinil | Avoid concomitant use<br>(may reduce efficacy) |

**Pharmacokinetics**

| | |
|---|---|
| **Effect of food** | High-fat & high-calorie meal delay $T_{max}$ & reduce $C_{max}$<br>(does not appear to affect total exposure - AUC) |
| **$T_{max}$** | 1–2 hours (lemborexant 1 to 3 hours) |
| **Half-life** | 8 hours |
| **Metabolism** | primarily metabolized by CYP3A4 |
| **Excretion** | Urine (28%); feces (57%) primarily as metabolites |

**"Clinical Efficacy**

- The efficacy of Quviviq for the treatment of insomnia was evaluated in two multicenter, randomized, double-blind, placebo-controlled, parallel-group trials in 1,854 adult patients with Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5®) insomnia for a duration of three months. Study 1 evaluated the 25 mg and 50 mg doses, whereas study 2 evaluated a 25 mg and 10 mg (non-FDA-approved) dose.
- The primary efficacy endpoints were the change from baseline to month 1 and month 3 in Latency to Persistent Sleep (LPS) and Wake After Sleep Onset (WASO), measured by polysomnography in a sleep laboratory. LPS is a measure of sleep induction and WASO is a measure of sleep maintenance.
- In study 1, Quviviq 25 mg and 50 mg demonstrated a statistically significant difference vs. placebo on polysomnography in WASO and LPS at months 1 and 3.
    - Treatment difference in WASO vs. placebo
        - Month 1: 50 mg: -23 min, $p < 0.05$, 95% Confidence Interval (CI) [-28, -18]; 25 mg: -12 min, $p < 0.05$, 95% CI [-17, -7]
        - Month 3: 50 mg: -18 min, $p < 0.05$, 95% CI [-24, -13]; 25 mg: -12 min, $p < 0.05$, 95% CI [-17, -6]
    - Treatment difference in LPS vs. placebo
        - Month 1: 50 mg: -11 min, $p < 0.05$, 95% CI [-16, -7]; 25 mg: -8 min, $p < 0.05$, 95% CI [-13, -4]
        - Month 3: 50 mg: -12 min, $p < 0.05$, 95% CI [-16, -7]; 25 mg: -8 min, $p < 0.05$, 95% CI [-12, -3]
- In study 2, Quviviq 25 mg demonstrated a statistically significant difference vs. placebo on polysomnography in WASO at month 1 (treatment difference 25 mg: -12 min, $p < 0.05$, 95% CI [-18, -6] and month 3 (treatment difference 25 mg: -10 min, $p < 0.05$, 95% CI [-17, -4]). Quviviq 25 mg did not show a statistically significant improvement in LPS at month 1 or month 3"

**Comments/Role in Therapy**

- Daridorexant is the 3rd FDA approved dual orexin receptor antagonist for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance
- Like the other 2 DORAs, lemborexant & suvorexant, daridorexant improves both subjective and objective measures of sleep onset & sleep maintenance compared with placebo
    - In 2 randomized 12 weeks trials (N=1854), daridorexant 25 to 50 mg nightly was significantly better than placebo for improving sleep maintenance & increasing total sleep time
- Daridorexant was approved in the European Union in April 2022 and was the first DORA to become available in Europe. It may offer another treatment option in adult patients with insomnia

- Daridorexant does not carry a black box warning, whereas, zolpidem, eszopiclone, and zaleplon have a black box warning for complex sleep behaviors
- The 2017 American Academy of Sleep Medicine Clinical Practice Guidelines recommend
    - suvorexant & doxepin for sleep maintenance insomnia
    - eszopiclone, zolpidem, & temazepam for sleep onset and sleep maintenance insomnia, and
    - zaleplon, triazolam, & ramelteon for sleep onset insomnia
- Guidelines have not been updated to include daridorexant, but will likely be recommended like suvorexant for use in patients with sleep maintenance insomnia
- DORAs are probably similar in potency to benzodiazepine receptor agonists for sleep maintenance insomnia
    - slightly better safety profile (does not appear to carry risks of respiratory depression)
    - cost may be a limiting factor
- Daridorexant has the shortest half-life (~8 hours) among the 3 dual orexin receptor antagonists. It has been promoted as a drug designed to improve potency and maximize duration of action while minimizing next-morning residual activity
- Pt education
    - The most common side effect is drowsiness the next day. It's important to be cautious since morning drowsiness can affect driving safety, job performance, and decision-making
- All DORAs are Schedule IV controlled substances
    - low abuse potential and do not appear to cause respiratory depression (not evaluated in pts with severe lung disease or severe sleep apnea)

**Comparison of Orexin Receptor Agonists**

| Drug (brand) | Dose (elderly ≥65 yo) | Dosing Regimen | Half-life | Significant DDIs |
|---|---|---|---|---|
| **Lemborexant (Dayvigo)** | 5 to 10 mg (5 mg) | 5 mg QHS taken within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening<br>If the 5 mg dose is well-tolerated but not effective, the dose can be increased, not to exceed 10 mg once daily | Long (17 – 19 hours) | • clearance dependent on CYP3A4<br>• recommended dose 5 mg, if used in combination with mild CYP3A4 inhibitors<br>• Avoid use with moderate and strong CYP3A4 inhibitors or inducers |
| **Suvorexant (Belsomra)** | 10 to 20 mg (10 to 15 mg) | 10 mg QHS taken within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening<br>If the 10 mg dose is well-tolerated but not effective, the dose can be increased, not to exceed 20 mg once daily | Intermediate (12 hours) | • clearance largely dependent on CYP3A<br>• recommended dose 5 mg (may increase to 10 mg), if used in combination with moderate CYP3A4 inhibitors<br>• Avoid use with strong CYP3A4 inhibitors or inducers |
| **Daridorexant (Quviviq)** | 25 to 50 mg (25 to 50 mg) | • 25 or 50 mg within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening<br>• 50 mg is an appropriate initial | Intermediate (8 hours) | • clearance largely dependent on CYP3A<br>• recommended dose 25 mg, if used in combination with moderate CYP3A4 inhibitors |

| | | | | |
|---|---|---|---|---|
| | | dose that appears to be equally safe & somewhat more effective than 25 mg | | Avoid use with strong inhibitors or moderate/strong CYP3A inducers |

**Pricing and Formulary Considerations:**

| Brand (generic) | Daily Dosage Range | Cost per 30 Days (WAC) | Formulary Status BHRS | Formulary Status CareAdvantage | Formulary Status DHCS |
|---|---|---|---|---|---|
| **Dayvigo (lemborexant)** | 5-10mg | $ 294 | PA required<br>QL #30/30DS | PA required | PA required |
| **Belsomra (suvorexant)** | 10-20mg | $ 408 | PA required<br>QL #30/30DS | Formulary<br>QL #30/30DS | PA required |
| **Quviviq (daridorexant)** | 25-50mg | $457 | PA required<br>QL #30/30DS | PA required<br>QL #30/30DS | PA required |

Wholesale Acquisition Cost (WAC) pricing from RxNova on 6/1/2022

All three DORAs are nonformulary on DHCS MediCal Formulary, requiring Prior Authorizations
HPSM CareAdvantage has Belsomra as formulary with QL
BHRS PA criteria for Belsomra and Dayvigo are:

Adults with diagnosis of insomnia
Tried and failed 3 formulary agents

**Recommend:**
**PA requirement for Quviviq for BHRS and Care Advantage, with similar approval criteria**

- **Adults with diagnosis of insomnia**
- **Tried and failed 3 formulary agents**
- **QL #30/30DS**

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