NHS
Cheshire and Merseyside

DARIDOREXANT Tablets (Quviviq® ▼) for treating long term insomnia

The Cheshire and Merseyside Area Prescribing Group recommends the prescribing of DARIDOREXANT Tablets (Quviviq ® ▼), for treating long term insomnia in accordance with NICE TA922.

GREEN

Daridorexant is licensed for the treatment of adult patients with insomnia characterised by symptoms present for at least 3 months, and considerable impact on daytime functioning[1]. It is the only pharmacological treatment currently licensed for the treatment of long-term insomnia.[2]

NICE technology appraisal (TA) 922 recommends daridorexant as an option for treating insomnia in adults with symptoms lasting for 3 nights or more per week for at least 3 months, and whose daytime functioning is considerably affected only if:

- cognitive behavioural therapy for insomnia (CBTi) has been tried but not worked, or
- CBTi is not available or is unsuitable[2].

Prescribing information[1]

Dose and administration

The recommended dose for adults is one tablet of 50 mg once per night, taken orally in the evening within 30 minutes before going to bed. Daridorexant can be taken with or without food but taking it after a large meal may reduce its effect on sleep onset. Dose adjustment will be required if the patient is taking a moderate CYP3A4 inhibitor or has moderate hepatic impairment (see Patient Factors section). The maximum daily dose is 50 mg.

Assessment of Therapeutic Effects

The length of treatment should be as short as possible. **Response to treatment should be assessed** within 3 months of starting and treatment should be stopped in people whose long-term insomnia has not responded adequately. If treatment is continued, assess whether it is still working at regular intervals. Clinical data are available for up to 12 months of continuous treatment. Treatment can be stopped without down-titration.

Implementation notes

Prescribers may refer to the NICE Clinical Knowledge Summary - insomnia for further information about the assessment, diagnosis and management of insomnia.

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

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Effectiveness

***Mechanism of Action*[1]**

Daridorexant is a dual orexin receptor antagonist. Orexin neuropeptides act on orexin receptors to promote wakefulness. Daridorexant antagonises the activation of orexin receptors and thereby decreases the wake drive, allowing sleep to occur, without altering the proportion of sleep stages.

***50mg Dose*[2]**

Daridorexant was studied in a phase 3 double-blind randomised controlled trial. 930 participants randomly assigned to receive daridorexant 25mg (n=310), 50mg (n=310) or placebo (n=310) for 12 weeks. Participants had a diagnosis of insomnia disorder (DSM-5 criteria) and insomnia severity score (ISI) of at least 15. The primary end points were wake after sleep onset (WASO) from baseline to month 1 and month 3 and latency to persistent sleep (LPS) from baseline to month 1 and month 3. The total follow-up time was 12 months. There were greater reductions from baseline in WASO and LPS for daridorexant 50mg compared with placebo at month 1 and month 3. WASO least squares mean (LSM) difference 22.78 minutes ($p<0.0001$) at 1 month and 18.30 minutes ($p<0.0001$) at three months. Reductions from baseline in ISI score were greater for daridorexant 50 mg than placebo. After 1 month the reduction from baseline in mean ISI score was 4.9 (standard deviation [SD] 5.5) for daridorexant and 3.1 (SD 4.7) for placebo. At month 3, the reduction from baseline in mean ISI score was 7.2 (SD 6.5) for daridorexant and 5.4 (SD 5.7) for placebo.

***25mg Dose*[3]**

In a phase 2, randomised, double-blind, placebo-controlled and active-controlled dose–response study 360 participants were randomly assigned to have placebo (n=60), daridorexant 5 mg (n=60), 10 mg (n=59), 25 mg (n=60), 50 mg (n=61) or zolpidem 10 mg (n=60) for 30 days. Participants had a diagnosis of insomnia disorder (DSM-5 criteria) and a self-reported history of ≥30 minutes latency to sleep onset (LSO), ≥30 minutes WASO, a total sleep time (TST) ≤ 6.5 hours on at least 3 of 7 consecutive nights, a bedtime between 21:30 and 00:30 hours and an ISI of at least 15. Mean reductions from baseline were observed for WASO (primary endpoint) and LPS (secondary endpoint) in all treatment groups on days 1 and 2. These improvements were sustained on days 28 and 29. In a second phase 3 double-blind randomised controlled (same design as that described above) trial 924 participants with long-term insomnia were randomly assigned to daridorexant 10 mg (n=307), 25 mg (n=309) or placebo (n=308) for 12 weeks. The total follow-up time was 12 months. There were greater reductions from baseline in WASO and LPS (latter not statistically significant) for daridorexant 25mg compared with placebo at month 1 and month 3.

Safety[1]

Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Narcolepsy
- Concomitant use with strong CYP3A4 inhibitors

Warning and Precautions

- Because of the general risk of falls in the elderly, daridorexant should be used with caution in this population.
- Patients should be warned about engaging in potentially hazardous activities, driving, or operating heavy machinery unless they feel fully alert, especially in the first few days of treatment. A period of approximately 9 hours is recommended between taking daridorexant and driving or using machines.
- Caution should be exercised when prescribing concomitantly with CNS-depressant medicines – potential for additive effects. Dose adjustment of either daridorexant or the concomitant CNS-depressants should be considered. Other hypnotic medicines should be reviewed prior to starting daridorexant and, if they are to be stopped or reduced, this should be done in accordance with clinical recommendations e.g. Clinical Knowledge Summary - Benzodiazepine and z-drug withdrawal
- 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 daridorexant, mainly during the first weeks of treatment. Symptoms similar to mild cataplexy have been reported with dual orexin receptor antagonists. Prescribers should explain the nature of these events to patients when prescribing. If they occur, patients need to be further evaluated and, depending on the nature and severity of the events, discontinuation of treatment should be considered.

- Patients should be warned about drinking alcohol during treatment (additive effects on psychomotor performance).
- Administer with caution in patients exhibiting symptoms of depression. Isolated cases of suicidal ideation have been reported in subjects with pre-existing psychiatric conditions and/or stressful living conditions. Suicidal tendencies may be present in patients with depression and protective measures may be required.
- There are limited safety and efficacy data for patients with psychiatric co-morbidities.
- Daridorexant should be used with caution in patients with severe obstructive sleep apnoea (OSA) and/or severe COPD.
- There was no evidence of abuse or withdrawal symptoms indicative of physical dependence upon treatment discontinuation in clinical studies with daridorexant in subjects with insomnia. In an abuse liability study conducted in non-insomniac recreational drug users daridorexant (100 and 150 mg) produced similar "drug liking" ratings as zolpidem (30 mg). Because individuals with a history of abuse or addiction to alcohol or other substances may be at increased risk for abuse of daridorexant, these patients should be followed carefully.

Side Effects

- Headache
- Somnolence

Refer to product SmPC for complete list of contraindications, warnings, cautions and side effects.

Cost

The cost per patient per annum using either 25mg or 50mg dose is £511 (excluding VAT).[4]

Based on the NICE Resource Impact Template, NICE estimates the cost of implementing NICE TA922 as £10,000 per 100,000 population in 2023/24, £19,000 per 100,00 population in 2024/25, £30,000 per 100,000 population in 2025/26, 43,000 per 100,000 population in 2026/27, rising to £56,000 per 100,000 population by the end of 2027/28 when it is assumed that steady state will have been reached.

Patient factors[1]

Hepatic Impairment

Mild hepatic impairment - no dose adjustment is required.
Moderate hepatic impairment - recommended dose is 25 mg at night.
Severe hepatic impairment - not recommended.

Renal Impairment

In patients with renal impairment (including severe), no dose adjustment is required.

Interactions

The recommended dose when used with moderate CYP3A4 inhibitors is 25 mg at night.
The consumption of grapefruit or grapefruit juice in the evening should be avoided.
Refer to product SmPC for complete list of interactions.

Patient Age

No dose adjustment is required in elderly patients (> 65 years). Limited data are available in patients older than 75 years. No data are available in patients older than 85 years.

Pregnancy

There are no data on the use of daridorexant in pregnant women. Animal studies did not indicate harmful effects with respect to reproductive toxicity. Daridorexant should be used during pregnancy only if the clinical condition of the pregnant woman requires treatment with daridorexant.

Breastfeeding

It is unknown whether daridorexant or its metabolites are excreted in human milk. Available data in animals have shown excretion of daridorexant and its metabolites in milk. A risk of excessive somnolence to the breastfed infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue daridorexant therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

References

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3. Single Technology Appraisal Daridorexant for treating insomnia [ID3774] Committee Papers. Available at TA922 Daridorexant for treating long-term insomnia: final appraisal determination committee papers 18/10/2023 (nice.org.uk). Accessed 17 November 2023.
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