Evidence and guidance in treating adults with long-term insomnia

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TA922

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Evidence and guidance for the use of QUVIVIQ™▼ (daridorexant) in treating adults with long-term insomnia

Daridorexant for treating long-term insomnia [TA922] (published 18th October 2023)

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This document aims to explain the role of daridorexant for the treatment of long-term insomnia.

Daridorexant is indicated for the treatment of adult patients with insomnia characterised by symptoms present for at least 3 months and a considerable impact on daytime functioning.[2]

NICE recommendation for daridorexant[1]

Daridorexant is recommended 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

The length of treatment should be as short as possible. Treatment with daridorexant should be assessed within 3 months of starting and should be stopped in patients whose long-term insomnia has not responded adequately. If treatment is continued, assess whether it is still working at regular intervals.

This recommendation is not intended to affect treatment with daridorexant started in the NHS prior to the publication of this guidance.[1] Patients receiving treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.[1]

Treatment pathway for insomnia

Patients with long-term insomnia are offered sleep hygiene advice, followed by CBTi as the recommended first-line treatment.[1] Access to CBTi varies geographically, with some patients experiencing difficulties accessing this treatment. Clinical experts state that CBTi has a 70% to 80% response rate, and roughly 50% of people whose condition responds positively to it experience long-term

Table 1
Inclusion and exclusion criteria for participants in study 301 and 303

Inclusion criteria	Exclusion criteria
• A diagnosis of insomnia disorder (referred to as long-term insomnia in this guidance) according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) criteria • An ISI score of at least 15	• Concomitant CBTi unless started at least 1 month before visit 3 (baseline time point) and continued throughout the study • Mental health conditions diagnosed by the Mini International Neuropsychiatric Interview as 'acute or unstable' • Concomitant CYP3A4 inhibitors

remission.[1] However, patients may either not have access to online CBTi, or struggle to use it.[1] NICE medical technologies guidance also recommends Sleepio – a self-help digital sleep improvement program for insomnia and associated symptoms.[3] Following NICE guidance, daridorexant is now recommended for the treatment of adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning if CBTi has been tried but hasn't worked, or if CBTi is not available or is unsuitable.[1]

Clinical trial results for daridorexant[1]

The clinical effectiveness of daridorexant 50mg was assessed in study 301 and extension study 303, with additional evidence assessing the clinical effectiveness of daridorexant 25mg presented in studies 302 and 201.

Clinical effectiveness of daridorexant 50mg

Study 301

Study 301 was a phase 3 double-blind randomised controlled trial with 930 people with long-term insomnia. Eligible participants (see table 1 for inclusion/exclusion criteria) were randomly assigned to have daridorexant 25mg (n=310), daridorexant 50mg (n=310) or placebo (n=310) for 12 weeks. Ethnicity of participants was 89.5% White, 9.5% Black, and 1.0% Asian. The primary efficacy endpoints were change in objective wake after sleep onset (WASO) from baseline to month 1 and month 3 and change in objective latency to persistent sleep (LPS) from baseline to month 1 and month 3. An insomnia severity index (ISI) score was used as an exploratory outcome and informed economic modelling.

Clinical effectiveness of daridorexant 50mg on WASO and LPS

Study 301 showed greater reductions from baseline in WASO and LPS for daridorexant 50mg compared with placebo at month 1 and 3 (table 2).

Table 2
Clinical effectiveness of daridorexant 50mg on WASO and LPS

	LSM difference between 50mg daridorexant and placebo	
	Month 1	Month 3
WASO	22.78 minutes (p<0.0001)	18.30 minutes (p<0.0001)
LPS	11.35 minutes (p<0.0001)	11.67 minutes (p<0.0001)

LPS: latency to persistent sleep; LSM: least squares mean; WASO: wake after sleep onset

Effect of daridorexant 50mg on ISI score
In study 301, reductions from baseline in ISI score were greater for daridorexant 50mg than placebo at both month 1 and month 3 (table 3). At 3 months, a between-arm analysis for ISI score showed a mean difference of -1.8 (95% confidence interval 2.74 to -0.85).

Table 3
Effect of daridorexant 50mg on ISI score

	Reduction from baseline in mean ISI score	
	Month 1	Month 3
DARIDOREXANT	4.9 (SD 5.5)	7.2 (SD 6.5)
PLACEBO	3.1 (SD 4.7)	5.4 (SD 5.7)

ISI: insomnia severity index; SD: standard deviation

Effect of daridorexant 50mg on other exploratory outcomes
For most exploratory outcomes, daridorexant 50mg showed a statistically significant reduction in insomnia compared with placebo at 3 months, but the benefits for some outcomes did not persist at 12 months (the exact outcomes are considered confidential and cannot be reported here). As there were no clinical data beyond 12 months, there is uncertainty about the duration and extent of benefit of treatment beyond 12 months.

Clinical effectiveness of daridorexant 25mg

Study 201
Study 201 was a phase 2, randomised, double-blind, placebo-controlled, and active-controlled dose–response study for patients with long-term insomnia (n=360). Participants were randomised to have placebo (n=60), daridorexant 5mg (n=60), 10mg (n=59), 25mg (n=60), 50mg (n=61) or zolpidem 10mg (n=60) for 30 days.

Study 302
Study 302 was a phase 3 double-blind randomised controlled trial. 924 patients with long-term insomnia were randomly assigned to have daridorexant 10mg (n=307), daridorexant 25mg (n=309) or placebo (n=308) for 12 weeks.

Clinical effectiveness of daridorexant 25mg on WASO and LPS
Studies 201 and 302 showed greater reductions from baseline in WASO for daridorexant 25mg compared with placebo (table 4). For LPS, both studies showed improvement from baseline for daridorexant 25mg compared with placebo, however this was not statistically significant at month 1 or 3 in study 302.

Table 4
Clinical effectiveness of daridorexant 25mg on WASO

	LSM difference between 25mg daridorexant and placebo		
	Days 1 & 2	Month 1	Month 3
WASO	-16.2 minutes (p=0.007)	-11.62 minutes (p=0.0001)	10.25 minutes (p=0.0028)

LSM: least squares mean; WASO: wake after sleep onset

Effect of daridorexant 25mg on ISI score
The absolute change in ISI score from baseline to day 30 was similar between placebo and daridorexant in study 201 (table 5). In study 301, the absolute change from baseline to month 3 was similar between placebo and daridorexant (table 5). In study 302, daridorexant 25mg demonstrated greater reduction in mean ISI scores from baseline at both month 1 and month 3 compared with placebo (table 5).

Table 5
Effect of daridorexant 25mg on ISI score

	Absolute change in ISI score		
	Baseline to day 30 (study 201)	Baseline to month 3 (study 301)	Baseline to month 1 and month 3 (study 302)
DARIDOREXANT	-7.9 (SD 5.9)	-6.0 (SD 5.8)	-5.1 (SD 5.2) and -6.9 (SD 6.0)
PLACEBO	-7.7 (SD 5.4)	-5.4 (SD 5.7)	-3.8 (SD 4.6) and -5.4 (SD 5.5)

ISI: insomnia severity index; SD: standard deviation

Effect of daridorexant 25mg on other exploratory outcomes
In study 201, the 25mg daridorexant dose showed higher mean self-reported visual analogue scale (VAS) scores for sleep quality, morning sleepiness, and daytime alertness compared with placebo. In summary, daridorexant 25mg was less clinically effective than 50mg. In study 302, subjective assessments of insomnia severity and sleep quality indicated benefits for daridorexant 25mg. Changes from baseline in VAS scores from the Sleep Disorders Questionnaire (SDQ; quality and depth of sleep, daytime alertness, ability to function) were greater for daridorexant 25mg than for placebo.

Study 303
Study 303 was primarily a comparative safety study that included placebo-controlled subjective outcomes to assess the long-term maintenance effect of daridorexant (see table 1 for inclusion/exclusion criteria). Participants in study 303 had already been participants in either study 301 or study 302. Participants who received daridorexant in study 301 or 302 continued to receive the same dose, either 25mg (n=268) or 50mg (n=137). Those assigned to placebo in study 301 or study 302 were re-randomised to have either placebo (n=128) or daridorexant 25mg (n=126). Ethnicity of participants was 89.5% White, 8.5% Black, and 1.0% Asian. The treatment period lasted 40 weeks in study 303 (total follow-up time from study 301 and study 303 was 12 months). The primary outcome measure was the total number of people with at least 1 treatment-emergent adverse event. An ISI score was used as an exploratory efficacy outcome and informed the economic modelling.

Safety results

Although daridorexant has a better safety profile than some other treatments, some are considered equally safe. There were no additional safety advantages or concerns associated with the 25mg daridorexant dose compared with the 50mg daridorexant dose (table 6).

Longer-term treatment effect of daridorexant
The long-term effect of daridorexant is uncertain, due to a lack of trial evidence on daridorexant treatment effect beyond 12 months.

Table 6
Adverse event reporting

Participants with treatment-emergent adverse events

	Study 301	Study 303
DARIDOREXANT 25MG	37.7%	37.7%
DARIDOREXANT 50MG	37.7%	38.0%
PLACEBO	34.0%	33.6%
EX-PLACEBO TO 25MG ARM	–	38.1%

Participants with treatment-emergent serious adverse events

	Study 301	Study 303
DARIDOREXANT 25MG	0.6%	4.5%
DARIDOREXANT 50MG	1.0%	5.1%
PLACEBO	2.3%	1.6%
EX-PLACEBO TO 25MG ARM	–	3.2%

Posology of daridorexant for treating long-term insomnia
Daridorexant 25mg is indicated for people with moderate liver impairment or who are taking moderate CYP3A4 inhibitor drugs. In clinical practice, clinical experts state that GPs are likely to start from the lower 25mg dose and titrate up to the 50mg dose if necessary. Based on clinical expert opinion, the committee considered that people without liver problems or not taking CYP3A4 inhibitor drugs may still start on the 25mg dose.

Prescribing of daridorexant for long-term insomnia
The NICE evaluation committee noted that daridorexant would be offered mainly in primary care by GPs.

Cost effectiveness analysis of daridorexant for long-term insomnia
Accounting for some uncertainty about the cost-effectiveness modelling assumptions for daridorexant and its benefits compared with placebo beyond 12 months, the most plausible incremental cost-effectiveness ratio was sufficiently close to the threshold NICE considered to be an acceptable use of NHS resources.

Implementation

Integrated care boards, NHS England and local authorities are required to comply with recommendations in the NICE guidance within 3 months of its date of publication. When NICE recommends a treatment 'as an option', the NHS must make sure it is available within this period. Therefore, if a patient has long-term insomnia and the doctor responsible for their care thinks that daridorexant is the right treatment, it should be available for use, in line with NICE's recommendations.

The importance of treating insomnia

Long-term insomnia has both night-time symptoms and an effect on daytime functioning, which can substantially affect quality of life. Comments from a patient

Key points

- Clinical trial evidence shows that daridorexant improves symptoms of insomnia compared with placebo at 3 months, with data out to 12 months, and provides a valuable treatment option for clinicians.
- Daridorexant is recommended 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 CBTi has been tried but not worked, or CBTi is not available or is unsuitable.
- The NICE evaluation committee noted that daridorexant would be offered mainly in primary care by GPs.

expert described insomnia as more than just struggling to sleep – insomnia has adverse effects on mental and physical health, emotional wellbeing, and social relationships. The patient expert also highlighted that people with insomnia may receive different care depending on where they live.

References

1. NICE. *Daridorexant for treating long-term insomnia* [TA922]. 2023. Available at: https://bit.ly/3uBX0Sh. Accessed June 2024.
2. QUVIVIQ™ Idorsia Pharmaceuticals LTD, Summary of Product Characteristics.
3. NICE. *Sleepio to treat insomnia and insomnia symptoms*. 2022. Available at: https://bit.ly/47JWqjS. Accessed June 2024.

Prescribing Information
Great Britain and Northern Ireland
QUVIVIQ ▼25 mg and 50 mg film-coated tablets (daridorexant)

Important note: Before prescribing, consult the full SmPC.

Presentation
Daridorexant 25 mg and 50 mg film-coated tablets

Therapeutic indication
QUVIVIQ is indicated for the treatment of adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning.

Posology and method of administration
Recommended dose: one tablet of 50 mg once per night, taken orally in the evening within 30 minutes before going to bed. The maximum daily dose is 50 mg.

For patients with moderate hepatic impairment, or taking moderate CYP3A4 inhibitors, or CNS depressants (based on clinical judgement) the recommended dose is 25 mg once per night.

The treatment duration should be as short as possible. The appropriateness of continued treatment should be assessed within 3 months and periodically thereafter. Clinical data are available for up to 12 months of continuous treatment.
If a dose is forgotten at bedtime, that dose should not be taken during the night. The consumption of grapefruit or grapefruit juice in the evening should be avoided.

Contraindications
- Hypersensitivity to daridorexant or any of the excipients
- Narcolepsy
- Concomitant use with strong CYP3A4 inhibitors

Warnings and precautions for use
Use with caution in elderly patients because of the general risk of falls although clinical studies did not show an increase in the incidence of falls on daridorexant compared to placebo. Efficacy and safety data in patients >75 are limited.

Patients should be cautioned about drinking alcohol during treatment.

Use with caution when prescribing with CNS-depressant medicinal products due to potentially additive effects and consider a dose adjustment of either QUVIVIQ or the CNS depressant.

Sleep paralysis and hypnagogic/hypnopompic hallucinations can occur, mainly during the first weeks of treatment. Symptoms similar to mild cataplexy have been reported with dual orexin receptor antagonists. Prescribers should explain this to patients and should consider discontinuing treatment depending on the nature and severity of any events.

Use with caution in patients exhibiting symptoms of depression. Suicidal tendencies may be present in patients with depression and protective measures may be required.

Use with caution in patients with psychiatric co-morbidities due to limited efficacy and safety data.

Daridorexant did not have significant respiratory effects in patients with mild to moderate or severe obstructive sleep apnoea (OSA) or moderate chronic obstructive pulmonary disease (COPD). In the absence of data, use with caution in patients with 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. Because individuals with a history of abuse or addiction to alcohol or other substances may be at increased risk for abuse of QUVIVIQ, these patients should be followed carefully.

Use is not recommended in patients with severe hepatic impairment.

Interactions
Contraindicated with strong CYP3A4 inhibitors. Use with moderate or strong CYP3A4 inducers may reduce efficacy. Caution should be used in case of simultaneous administration of QUVIVIQ with sensitive substrates of CYP3A4, or of P-gp, with close monitoring in the case of medicinal products with a narrow therapeutic index (e.g. digoxin). The consumption of grapefruit or grapefruit juice in the evening should be avoided. Refer to full SmPC for further information on interactions.

Fertility, pregnancy and lactation
Use during pregnancy only if the clinical condition of the pregnant woman requires treatment with QUVIVIQ.

Available data indicates that the presence of daridorexant in breast milk is low. Consider discontinuing breast-feeding or QUVIVIQ because a risk of excessive somnolence to the breastfed infant cannot be excluded.

Effects on ability to drive and use machines
Patients should be cautioned about engaging in potentially hazardous activities, driving, or operating heavy machinery unless they feel fully alert, especially in the first few days of treatment. In order to minimise this risk, a period of approximately 9 hours is recommended between taking QUVIVIQ and driving or using machines.

Undesirable effects
Common (≥ 1/100 to < 1/10): headache, somnolence, dizziness, nausea, fatigue.
Consult the full SmPC for further information on side effects.

Overdose
General symptomatic and supportive medical care should be provided. Adverse reactions at supra-therapeutic doses may include somnolence, muscular weakness, disturbance in attention, fatigue, headache and constipation.

Packaging quantity and storage conditions
Blisters packed in cartons of 10 or 30 film-coated tablets.

Marketing Authorisation Holder and Numbers
Idorsia Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

Great Britain: PLGB 48711/0002-0003
Northern Ireland: EU/1/22/1638/001-006

Cost
QUVIVIQ 25 mg x 30 tablets and QUVIVIQ 50 mg x 30 tablets: £42 per pack

Prescription conditions
Prescription only medicine.

UK-DA-00157
Date of last revision of prescribing information
May 2024

Adverse events must be reported. Healthcare professionals are asked to report any suspected adverse reactions via www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in Google play or Apple App store. Adverse events should also be reported to ds.safety.uk@idorsia.com

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