SMC2611

# daridorexant film-coated tablets (Quviviq®)

## Idorsia Pharmaceuticals UK Ltd

08 March 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

**ADVICE**: following a full submission

**daridorexant (Quviviq®)** is accepted for restricted use within NHSScotland.

**Indication under review:** treatment of adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning.

**SMC restriction:** in patients who have failed cognitive behavioural therapy for insomnia (CBT-I) or for whom CBT-I is unsuitable or unavailable.

Daridorexant, compared with placebo, improved time to fall asleep and waking after sleep onset in adults with insomnia.

Overleaf is the detailed advice on this product.

**Chair**
**Scottish Medicines Consortium**

# 1. Clinical Context

### 1.1. Medicine background

Daridorexant is an antagonist of orexin 1 and orexin 2 receptors, which limits the activity of the orexin neuropeptides (orexin A and orexin B) that act on these receptors to promote wakefulness. Consequently, daridorexant decreases the wake drive, allowing sleep to occur, without altering the proportion of sleep stages. The recommended dose is daridorexant 50 mg orally in the evening about 30 minutes before bed. Based on clinical judgement, daridorexant 25 mg can be used for some patients, such as those with hepatic impairment or receiving moderate CYP3A4 inhibitors. Refer to Summary of Product Characteristics. Treatment duration should be as short as possible. The appropriateness of continued treatment should be assessed within 3 months and periodically thereafter.[1]

### 1.2. Disease background

Insomnia is characterised by dissatisfaction with sleep quantity or quality, with difficulty initiating sleep and/or maintaining sleep and early-morning awakening with inability to return to sleep. It can be distressing and impair daytime functioning.[2]

### 1.3. Company proposed position

The submitting company has requested that SMC consider daridorexant when positioned for use in patients who have failed cognitive behavioural therapy for insomnia (CBT-I) or for whom CBT-I is unsuitable or unavailable.

### 1.4. Treatment pathway and relevant comparators

The recommended first-line treatment for insomnia is CBT-I. Alternative options include hypnotic medicines, such as benzodiazepines, non-benzodiazepine GABA-A receptor agonists (referred to as 'z-drugs' such as zolpidem), melatonin, and off-label sedating antidepressants and antihistamines. These medicines are usually given as short-term treatment or a temporary adjunct to CBT-I.[2] Clinical experts consulted by SMC did not provide a consensus on a treatment pathway. Some note that benzodiazepines, non-benzodiazepine GABA-A receptor agonists and melatonin are used off-label for prolonged periods and melatonin may be given outside its licence in patients <55 years old.

# 2. Summary of Clinical Evidence

### 2.1. Evidence for the licensed indication under review

Clinical evidence comprised phase II data (Study 201) and phase III data (Studies 301 and 302 plus the extension to these, Study 303).[2-4]

**Table 2.1. Overview of relevant studies.[2-4]**

| Criteria | Study 301 | Study 302 |
|---|---|---|
| Study design | Double-blind, randomised, phase III studies | |
| Eligible patients | Age >18 years with insomnia disorder on DSM-5; sleep latency ≥30 minutes, WASO ≥ 30 minutes, and TST ≤6.5 hours for ≥3 nights per week for ≥3 months and for ≥3 of 7 nights in placebo run-in. Insomnia Severity Index (ISI) score ≥15 (moderate or severe). On polysomnography for two consecutive nights' in | |

| | | |
|---|---|---|
| | placebo run-in, mean LPS ≥ 20 minutes, with neither night < 15 minutes; mean WASO ≥30 minutes, with neither night <20 minutes; and mean sTST <7 hours. | |
| Treatments | Placebo or daridorexant 25 mg or 50 mg orally at night for 3 months | Placebo or daridorexant 10 mg or 25 mg orally at night for 3 months |
| Randomisation | Randomisation stratified by age (<65 versus ≥65 years); assigned in 1:1:1 ratio. | |
| Primary outcomes | Change at month 1 and 3 in WASO and LPS on polysomnography. | |
| Secondary outcomes | Change at month 1 and 3 in sTST and IDSIQ sleepiness domain score. | |
| Statistical analysis | Type 1 error controlled for the 8 primary and 8 key secondary outcomes using Bonferroni correction and gatekeeping. Efficacy was in all randomised patients. | |

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; IDSIQ = Insomnia Daytime Symptoms and Impacts Questionnaire; LPS = latency to persistent sleep; sTST = self-reported total sleep time; WASO = wake after sleep onset.

In Study 301, the primary and key secondary outcomes significantly improved with daridorexant 25 mg and 50 mg, compared with placebo, except for changes at Month 1 and 3 in the sleepiness domain score of the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) with the lower dose. For Study 302, results of the licensed lower dose of daridorexant (25 mg) are presented. Compared with placebo, daridorexant 25 mg significantly improved changes at Month 1 and 3 for one primary outcome, wake after sleep time (WASO) but not the other, latency to persistent sleep (LPS); and for one key secondary outcome, self-reported total sleep time (sTST), but not IDSIQ sleepiness domain.[2-4] Results of these and an exploratory outcome, Insomnia Severity Index (ISI), that supports the economic analysis, are detailed in Table 2.2.

**Table 2.2: Results of Study 301 and 302 (for licensed doses).[2-4]**

| | **Study 301** | | | **Study 302** | |
|---|---|---|---|---|---|
| | **Daridorexant 50 mg (n=310)** | **Daridorexant 25 mg (n=310)** | **Placebo (n=310)** | **Daridorexant 25 mg (n=309)** | **Placebo (n=308)** |
| **LSM change in Wake After Sleep Onset (WASO) time on polysomnography, minutes** | | | | | |
| **Month 1** | -29.0 | -18.4 | -6.2 | -24.2 | -12.6 |
| Difference (95% CI) | -22.8 (-28, -17.6)* | -12.2 (-17.4, -7.0)* | | -11.6 (-17.6, -5.6)* | |
| **Month 3** | -29.4 | -23.0 | -11.1 | -24.3 | -14.0 |
| Difference (95% CI) | -18.3 (-23.9, -12.7)* | -11.9 (-17.5, -6.2)* | | -10.3 (-17.0 to -3.5)* | |
| **LSM change in Latency to Persistent Sleep (LPS) time on polysomnography, minutes** | | | | | |
| **Month 1** | -31.2 | -28.2 | -19.9 | -26.5 | -20.0 |
| Difference (95% CI) | -11.4 (-16.0, -6.7)* | -8.3 (-13.0, -3.6)* | | -6.5 (-12.3, -0.6) | |
| **Month 3** | -34.8 | -30.7 | -23.1 | -28.9 | -19.9 |
| Difference (95% CI) | -11.7 (-16.3, -7.0)* | -7.6 (-12.3, -2.9)* | | -9.0 (-15.3, -2.7) | |
| **LSM change in self-reported Total Sleep Time (sTST), minutes** | | | | | |
| **Month 1** | 43.6 | 34.2 | 21.6 | 43.8 | 27.6 |
| Difference (95% CI) | 22.1 (14.4, 29.7)* | 12.6 (5.0, 20.3)* | | 16.1 (8.2, 24.0)* | |
| **Month 3** | 57.7 | 47.8 | 37.9 | 56.2 | 37.1 |
| Difference (95% CI) | 19.8 (10.6, 28.9)* | 9.9 (0.8, 19.1)* | | 19.1 (10.1, 28.0)* | |

| | | | | | |
|---|---|---|---|---|---|
| **LSM change in Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ) sleepiness domain** | | | | | |
| **Month 1** | -3.8* | -2.8 | -2.0 | -3.5 | -2.8 |
| Difference (95% CI) | -1.8 (-2.5, -1.0) | -0.8 (-1.5, 0.01) | | -0.8 (-1.6, 0.1) | |
| **Month 3** | -5.7* | -4.8 | -3.8 | -5.3 | -4.0 |
| Difference (95% CI) | -1.9 (-2.9, -0.9) | -1.0 (-2.0, 0.01) | | -1.3 (-2.2, -0.3) | |
| **LSM change in Insomnia Severity Index (ISI)** | | | | | |
| **Month 1** | -4.9 | -4.1 | -3.1 | -5.1 | -3.8 |
| **Month 3** | -7.2 | -6.0 | -5.4 | -6.9 | -5.4 |
| **Insomnia Severity Index (ISI) <10 (minimal to none), n (%)** | | | | | |
| **Month 1** | 61 (20) | 56 (19) | 33 (11) | 60 (21) | 40 (14) |
| **Month 3** | 100 (35) | 98 (34) | 71 (25) | 95 (34) | 64 (23) |

CI = confidence interval; LSM = least square mean. * statistically significant within the gatekeeping process controlling for type 1 error.

Upon completion of 301 and 302 studies, 804 patients entered a double-blind extension, Study 303, where they continued on their same dose of daridorexant, with patients from the placebo groups re-randomised to continue this or receive daridorexant 25 mg at night for 40 weeks. It primarily assessed safety. Benefits in exploratory efficacy outcomes were maintained in patients who remained on daridorexant. The change from baseline to Week 48 (extension Week 36), compared with placebo (n=68 to 70), with daridorexant 50 mg and 25 mg were 17.8 and 5.3 minutes for sTST (n=87 and n=170 in the respective dose groups); and -2.7 and -1.2 for IDSIQ sleepiness domain (n=87 and n=175), respectively.[2,5]

A double-blind, dose-finding phase II study (Study 201), recruited 360 adults (age 18 to 64 years) to similar criteria as Studies 301 and 302. They were equally randomised to oral once nightly zolpidem 10 mg, placebo or daridorexant 5 mg, 10 mg, 25 mg or 50 mg for 29 days. The study primarily investigated a dose-response relationship for daridorexant for change in WASO (on polysomnography) at days 1 and 2 and this was demonstrated. The effects of daridorexant were maintained at days 28 and 29. There was no statistical comparison with zolpidem. Results for the licensed doses of daridorexant (25 mg and 50 mg) and zolpidem at days 28 and 29 are detailed in Table 2.3.[2,6]

**Table 2.3: Results of Study 201 at Day 28 and 29 (for licensed doses).[6]**

| | **Zolpidem 10 mg (n=60)** | **Daridorexant 50 mg (n=61)** | **Daridorexant 25 mg (n=60)** | **Placebo (n=60)** |
|---|---|---|---|---|
| LSM change in WASO, minutes | -36.5 | -48.0 | -38.9 | -33.8 |
| LSM change in LPS, minutes | -45.1 | -35.8 | -37.9 | -28.4 |
| LSM change in TST, minutes | 78.0 | 81.6 | 75.1 | 60.0 |

Outcomes were measured on polysomnography and represent the mean of measurements on Day 28 and 29. LPS = latency to persistent sleep; LSM = least square mean; TST = total sleep time; WASO = wake after sleep onset.

### 2.2. Evidence to support the positioning proposed by the submitting company

There were no subgroup analyses by previous CBT-I. In Studies 301 and 302, the majority of patients had never received or been offered CBT-I for various reasons.[7,8] Therefore, the studies provide evidence in patients who do not have access to CBT-I but provide minimal evidence in patients who have failed CBT-I.

### 2.3. Health-related quality of life outcomes

Health-related quality of life was assessed using the patient-reported outcomes: IDSIQ (total score range 0 to 140) and visual analogue scales (VAS) that assessed sleep quality, depth of sleep, daytime alertness, and daily ability to function (from 0 to 100). On the IDSIQ, higher scores indicate greater burden of illness for daytime symptoms of insomnia across three domains: alert/cognition (range 0 to 60), mood (range 0 to 40) and sleepiness (range 0 to 40). For Studies 301 and 302, the benefits of daridorexant on IDSIQ sleepiness domain are detailed in Table 2.2 and placebo-corrected change at Month 3 in alert/cognition was -2.5 with daridorexant 50 mg and -0.9 to -1.7 with daridorexant 25 mg; and in the mood was -2.8 with daridorexant 50 mg and -1.3 to -1.6 with daridorexant 25 mg. Results for the VAS were consistent with other outcomes.[2,3]

In studies 301 and 302, subjective benefits (reported by the patient) of daridorexant on waking during the night were smaller than those assessed on polysomnography. At Month 3, with daridorexant 50 mg and 25 mg, compared with placebo, reduction on self-reported WASO (sWASO) were 4.8 minutes and 5.1 to 6.9 minutes, respectively.[2]

The ISI assessed the severity of a patient's insomnia by scoring the severity of sleep onset and sleep maintenance difficulties and any insomnia-related interference with daytime functioning. It includes seven dimensions, each scored on a 5-point scale (0–4), that are summed to a composite score indicative of the patient's perception of insomnia severity: 15 to 21 indicates moderate; 22 to 28 indicates severe; and <10 indicates minimal-to-none. The mean change in ISI and proportion of patients achieving an ISI score <10 are detailed in Table 2.2 above.[2]

## 3. Summary of Safety Evidence

The safety profile of daridorexant is characterised by mainly mild to moderate adverse effects, with small increases, compared with placebo, in headache, somnolence, fatigue, dizziness and nausea. The European regulatory review noted a potential abuse concern with daridorexant, but no evidence of a withdrawal syndrome on abrupt discontinuation.[2]

In pooled data from Studies 301 and 302, in the daridorexant 50 mg, 25 mg and placebo groups, 39% (120/308), 41% (254/618) and 36% (224/615) of patients, respectively, reported adverse events. Serious adverse events occurred in 0.6%, 0.8% and 1.6% of the respective groups, with 0.6%, 1.9% and 2.8% of patients discontinuing treatment due to adverse events.[4]

In pooled data from Studies 301 and 302, in the daridorexant 50 mg, 25 mg and placebo groups, common adverse events included: headache (6.5%, 5.2% and 3.7%); nasopharyngitis (7.8%, 6.6% and 7.0%), fatigue (2.6%, 2.9% and 0.7%); somnolence (1.9%, 3.4% and 1.8%); dizziness (2.3%, 2.1% and 1.1%), nausea (2.6%, 0.8% and 1.1%) and diarrhoea (0.6%, 1.8% and 1.3%).[4]

## 4. Summary of Clinical Effectiveness Considerations

### 4.1. Key strengths

- In phase III studies (Study 301 and 302), at Month 3, with daridorexant 50 mg and 25 mg there were decreases compared with placebo in polysomnography-assessed LPS (time to persistent sleep) of 12 minutes (50 mg) and 8 to 9 minutes (25 mg); and in WASO (time awake after falling asleep) of 18 minutes and 10 to 12 minutes. Patients' perception of total sleep time improved, with increases in sTST, compared with placebo, of 20 minutes and 10 to 19 minutes with the respective doses, that were generally maintained in patients who continued treatment up to one year. The regulatory authority considered results for daridorexant 50 mg clinically relevant and for daridorexant 25 mg questionable.[2-4]
- Daridorexant is the first orexin receptor antagonist licensed in the UK for the treatment of insomnia.[1]

### 4.2. Key uncertainties

- At Month 3, patients' perceptions of daridorexant benefits on night-time waking (sWASO) appear smaller than those on polysomnography (WASO): with decreases, compared with placebo, of 4.8 minutes versus 18 minutes with daridorexant 50 mg and 5.1 to 6.9 minutes versus 10 to 12 minutes with daridorexant 25 mg.[2]
- Effects on daytime functioning appear modest, with mean IDSIQ improvements versus placebo for daridorexant 50 mg and 25 mg of 1.8 and 0.8 on a 40-point scale for sleepiness; 2.5 and 0.9 to 1.7 on a 60-point scale for alert/cognition; and 2.8 and 1.3 to 1.6 on a 40-point scale for mood. The European regulatory authority noted that the clinical relevance of these benefits is questionable. The proportion of patients achieving an ISI score <10 (that is, minimal or no insomnia symptoms) with daridorexant was around 10% greater than placebo.[2]
- The submitting company has requested that SMC consider daridorexant for use in two groups of patients: (a) those who have failed on CBT-I; and (b) those for whom CBT-I is unsuitable or unavailable. In Study 301 and 302, the majority of patients had never received or been offered CBT-I for various reasons.[7,8] The studies, therefore, provide evidence in the groups of patients for whom CBT-I is unsuitable or unavailable but provides minimal evidence in the group who have failed CBT-I.
- The submitting company considers that there is no relevant comparator within the proposed positioning. Clinical experts consulted by SMC did not provide a consensus on alternative treatment options in patients who have failed CBT-I or for whom this is unsuitable or unavailable. Some noted the off-label use of benzodiazepine, non-benzodiazepine GABA-A receptor agonists ('z-drugs' such as zolpidem) and melatonin. No direct or indirect comparative data versus these treatments was provided. Although zolpidem was included in the phase II Study 201, there was no formal comparison with daridorexant.[6]
- The mean time since diagnosis of insomnia was 10.2 to 11 years in Study 301 and 10.5 to 12.1 years in Study 302. Therefore, most of the patients in the studies had long-term

insomnia. There is no information on efficacy in patients who had suffered for shorter periods. As the studies excluded patients with mild insomnia and insomnia that could be explained by co-existing physical or mental health conditions or substance abuse, there is no evidence in these patients. In Studies 301 and 302, the majority of screened patients, 72% (2396/3326) and 75% (2759/3683), respectively, failed to meet inclusion and exclusion criteria. This may impact generalisability of results to the wider population of patients suffering insomnia.[3,7,8]

### 4.3. Clinical expert input

Clinical experts consulted by SMC generally considered that daridorexant fills an unmet need in this therapeutic area, namely a licensed medicine for chronic insomnia. Some note that it is a therapeutic advance due to its novel mechanism of action. The clinical experts advise that daridorexant may be used for patients who have failed CBT-I or for whom this is unsuitable or unavailable.

*Other data were also assessed but remain confidential.**

## 5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from The Sleep Charity, which is a registered charity.
- The Sleep Charity has received 6.9% pharmaceutical company funding in the past two years, including from the submitting company.
- Insomnia is a significant and debilitating sleep disorder that has far-reaching effects on people's lives. It impacts on people's mental and physical health. It also has effects in the workplace (on performance, productivity and absenteeism/presenteeism) and health & safety aspects including driver fatigue.
- The patient group described how there are large numbers of people who are struggling to get the help they need and are in crisis. They described how GPs may not be able to signpost them for CBT-I. In addition, even if available digital CBT-I is not always suitable for those with difficulties in accessing technology or those with disabilities.
- The patient group believe that access to daridorexant will help to improve the quality of life for some patients with potential improvements to physical and mental health and wellbeing and possible reductions in GP appointments for sleep related issues.

## 6. Summary of Comparative Health Economic Evidence

### 6.1. Economic case

A summary of the economic analysis performed by the submitting company is presented in Table 6.1.

**Table 6.1 Description of economic analysis**

| Criteria | Overview |
|---|---|
| Analysis type | Cost – utility analysis. |
| Time horizon | 1 year. |
| Population | Adult patients with insomnia characterised by symptoms present for at least 3 months and considerable impact on daytime functioning. The company adopted a selective positioning for the economic analysis of patients who have failed CBT-I (2nd line), or for whom CBT-I is unsuitable or unavailable (1st line). |
| Comparators | No pharmacological treatment. |
| Model description | A simple model design comparing costs and utility outcomes associated with differences in ISI score between daridorexant 50 mg vs no treatment over 12 months, split into defined time periods of 0, 1, 3, 6, 9 and 12 months. |
| Clinical data | Study 301 (for weeks 0-12) and the extension study 303 (weeks 12-52) provided ISI data for daridorexant and the placebo arm that was used as a proxy for the no treatment comparator. Analysis of the study 301 ISI data for the economic analysis used seemingly unrelated regression (SUR) analysis to adjust for baseline ISI and placebo.<br><br>Established clinical management (including sleep hygiene advice) was provided in both the daridorexant and placebo arms. Treatment-emergent adverse events occurring in >2% of patients in the clinical studies were included.<br><br>The ISI score improved from baseline to 12 months for both arms, with a larger improvement associated with the daridorexant arm. In the base case the intention to treat (ITT) analysis of ISI was used, hence there was no adjustment made for any potential placebo effect on ISI improvement in the no treatment comparator arm. |
| Extrapolation | In the base case no extrapolation was performed beyond the 12 months clinical study data. A lifetime horizon economic analysis assuming a constant treatment effect from 12 months onwards and taking relative risk of mortality associated with duration of sleep into account was performed as a scenario analysis. |
| Quality of life | A utility measure was not included in the daridorexant clinical studies hence statistical mapping of the relationship between ISI score and the EQ 5D-5L (with conversion to 3L utility values) was performed using the National Health and Wellness Survey (NHWS) observational study dataset which contained both measures self-reported in patients with insomnia from US, UK, Italy, Germany, France and Spain. A net utility gain was estimated for daridorexant vs no treatment over the 12-month time horizon. Account was taken of discontinuations from daridorexant and placebo arms on incremental utilities, assuming the discontinuation occurs at the midpoint of each time period in the model.<br><br>Account was also taken of adverse event disutilities for daridorexant. |
| Costs and resource use | A medicine acquisition cost of £1.40 per day was included for daridorexant taken as a daily tablet. For discontinuations, the cost of treatment was assumed to be incurred for the full period in which the discontinuation occurred.<br><br>Healthcare resource use costs were included for GP visits, A&E visits, inpatient stays, outpatient visits and concomitant medications. The NHWS dataset (UK patients only) was used to perform regression analysis to determine relationship between key healthcare resource use components and ISI score for patients with insomnia. Other costs included were for GP training on daridorexant use, and costs of adverse events management. |

### 6.2. Results

The base case results are shown in Table 6.2. These are based on taking account of discontinuations (ie assumes less than 100% persistence) over the 12 month time horizon.

**Table 6.2: Base case results**

| Technologies | Total | | Incremental | | ICER (£/QALY) |
|---|---|---|---|---|---|
| | Costs | QALYs | Costs | QALYs | |
| No treatment | £853 | 0.704 | | | |
| Daridorexant | £1,261 | 0.720 | £408 | 0.016 | £25,204 |

ICER = incremental cost-effectiveness ratio; QALY = Quality Adjusted Life Year

The key driver of incremental cost was the additional daridorexant drug cost, and additional QALYs was associated with the incremental improvements in ISI score over the 12-month time horizon. There was a small marginal cost and disutility associated with daridorexant AEs, and a small cost offset through reduced healthcare resource use associated with daridorexant.

### 6.3. Sensitivity analyses

Probabilistic sensitivity analysis (PSA), an atypical deterministic sensitivity analysis (stated to be based on the PSA whereby groups of parameters including those based on regression equations are varied, while holding all other parameters constant at base case values), and scenario analysis were performed. The probabilistic ICER was estimated at £25,226 per QALY gained with range of £14,521 - £69,327 per QALY gained based on 95% uncertainty intervals from the probabilistic analysis.

In deterministic sensitivity analysis the ICER was most sensitive to varying the ISI values estimated from study 303 (ICER range of £17,782 - £45,464 per QALY gained) and from study 301 (ICER range of £18,587 - £38,955 per QALY gained) with much smaller sensitivity associated with varying utilities or resource use parameters. Various scenario analyses were performed, including a scenario in which the ISI score for placebo was maintained rather than improved from 3 months to allow for observed selective attrition (defined as the selective drop out of patients who systematically differ from those remaining – ie drop outs have lower ISI improvement). This scenario and assuming 100% treatment persistence improved the ICER for daridorexant (Table 6.3). There was only a limited ICER impact from exploring long run cost-effectiveness. In scenario analyses including assessment of productivity costs daridorexant was estimated to dominate no treatment comparator (ie lower costs, higher QALYs).

**Table 6.3: Selected scenario analyses**

| | Parameter | Base case | Scenario | Incr. Costs (£) | Incr. QALYs | ICER (£/QALY) |
|---|---|---|---|---|---|---|
| | ***Base case*** | | | £408 | 0.016 | £25,204 |
| 1 | Discontinuations/ drop-outs | Included | 100% persistence assumed | £502 | 0.022 | £23,244 |
| 2 | Placebo effect | ITT: No adjustment for selective attrition | Assume no placebo ISI improvement after 3 months | £399 | 0.081 | £16,739 |
| 3 | Time horizon | 12 months | Lifetime | £3,510 | 0.15 | £23,429 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 4 | Costs | NHS costs only | Includes productivity costs* | -£188 | 0.016 | Dominant |

Abbreviations: ICER = incremental cost-effectiveness ratio; ITT = Intention to treat; QALY = Quality Adjusted Life Year; *Based on analysis of Sheenan Disability Scale (SDS) data in studies 301 and 303
Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.

### 6.4. Key strengths

- Time horizon of 12 months is appropriate and aligns with the comparative ISI outcomes data from study 301 and 303.
- The mapping of ISI score to EQ 5D utilities is robustly performed, subject to caveats outlined below regarding the NHWS dataset used.

### 6.5. Key uncertainties

- Daridoxetant has been positioned for use in two groups of patients who have failed CBT-I or for whom CBT-I is unsuitable or unavailable. However, almost all the patients included in the economic analysis from studies 301/303 had not previously received CBT-I, hence the cost-effectiveness of daridoxerant used second line in patients who have failed CBT-I is not clear.
- There is some uncertainty over the appropriate comparators, and whether off label use of benzodiazepines, z-drugs, and melatonin (extended use in patients under 55 years) should also be considered in the economic analysis.
- The ICER is dependent on differences in ISI score between daridorexant and placebo/ no treatment, with some potential limitations in these data from the clinical studies (the ISI was only included as an exploratory endpoint). The grouped parameter sensitivity analysis performed on ISI values in study 301 and 303 shows sensitivity in the ICER when varying these. The probabilistic analysis of the base case ICER also shows a large range hence uncertainty in the potential ICER, likely to be driven by relative ISI improvement uncertainty (£14,521 - £69,327/QALY).
- The handling of a possible placebo effect for the comparator arm has an impact on the cost-effectiveness. The base case uses ITT analyses for producing ISI score trajectories for daridorexant and placebo/ no treatment arms. A scenario was performed adjusting placebo to allow for selective attrition bias (scenario 2), which was based on more patients dropping out of the placebo arm than the daridorexant arm in study 303 with smaller relative ISI improvement than for the patients completing the study, hence potentially inflating the benefit in the placebo/ no treatment comparator. The ICER improved for this scenario compared to the base case, but the placebo adjustment performed was crude, therefore the potential ICER impact of assuming selective attrition is uncertain.
- The model structure has limitations based on a comparison of ISI score and related utility trajectories over time. The daridorexant SPC states that continued treatment with daridorexant should be reviewed within 3 months and periodically after. Hence, a model based on at least a 3 month continue or stop treatment structure may have been appropriate.

- The NHWS insomnia patient set used to estimate utilities and resource use were younger and had lower ISI scores compared to mean age and baseline ISI score of patients in the 301 study, so there may be some limitations in its generalisability to patients likely to be treated with daridorexant.
- The long term cost-effectiveness analysis is simple but lacks evidence to support a mortality benefit for daridorexant so is largely speculative, and there is high uncertainty associated with estimation of productivity benefits.

## 7. Conclusion

After considering all the available evidence, the Committee accepted daridorexant for restricted use in NHSScotland.

## 8. Guidelines and Protocols

In 2019, the British Association for Psychopharmacology published guidelines: British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders: An update.[9]

In 2017, the European Sleep Research Society published guidelines: European guideline for the diagnosis and treatment of insomnia.[10]

## 9. Additional Information

### 9.1. Product availability date

September 2023.

**Table 9.1 List price of medicine under review**

| Medicine | Dose regimen | Cost per year (£) |
|---|---|---|
| **Daridorexant** | **50mg (or 25mg if clinically indicated) at night** | **510** |

*Costs from BNF online on 16 November 2023.*

## 10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 93,131 patients eligible for treatment with daridorexant in each year. The estimated uptake was 2% in year 1 and 12% in year 5 with a discontinuation rate of 47% applied each year. This resulted in 1,017 patients in year 1 rising to 5,784 patients in year 5.

The gross medicines budget impact was estimated to be £520k in year 1 rising to £2.96m in year 5. As there were direct medical costs assumed to be saved, the net medicines budget impact was estimated to be £483k in year 1 and £2.75m in year 5.

SMC clinical expert responses estimate that the eligible population for daridorexant after CBT-I is lower than the 93,131 patients cited. Although expert responses also indicate that the uptake rate is likely to be higher than estimated by the submitting company.

**References**

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This assessment is based on data submitted by the applicant company up to and including 16 February 2024.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

*No part of this advice may be used without the whole of the advice being quoted in full.*

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.