NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Daridorexant for treating long-term insomnia

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using daridorexant in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using daridorexant in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 27 April 2023
- Second evaluation committee meeting: 4th May 2023
- Details of membership of the evaluation committee are given in section 4

1 Recommendations

1.1 Daridorexant is not recommended, within its marketing authorisation, for treating insomnia in adults with symptoms for at least 3 months and a considerable effect on daytime functioning.

1.2 This recommendation is not intended to affect treatment with daridorexant that was started in the NHS before this guidance was published. People having 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.

Why the committee made these recommendations

Cognitive behavioural therapy for insomnia (CBTi) is currently the standard first-line treatment for people with long-term insomnia after sleep hygiene advice is offered. But access to CBTi varies across the UK, sometimes it does not work, and sometimes it is unsuitable. Daridorexant may be another option for these people.

Clinical trial evidence shows that daridorexant improves symptoms of insomnia compared with placebo at 12 months. But the effects if it's taken for longer than this are unknown. There are also uncertainties in the economic model. The most likely cost-effectiveness estimate is above what NICE normally considers an acceptable use of NHS resources. So, daridorexant is not recommended.

2 Information about daridorexant

Marketing authorisation indication

2.1 Daridorexant (QUVIVIQ, Idorsia) 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'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for daridorexant.

Price

2.3 The list price of daridorexant has not yet been approved. The company have provided an anticipated list price, which is considered confidential until it has been approved.

3 Committee discussion

The evaluation committee considered evidence submitted by Idorsia, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 Long-term insomnia, also known as chronic insomnia or insomnia disorder, is defined as dissatisfaction with quantity or quality of sleep for 3 nights or above per week for at least 3 months with an effect on daytime functioning. Long-term insomnia has both night-time symptoms and an effect on daytime functioning. This affects subjective and objective dimensions of health. The patient expert described how insomnia negatively affects mental and physical health and emotional wellbeing. They explained that insomnia is more than struggling to sleep, it also affects daytime functioning and social relationships. The patient expert explained that people with insomnia may have different care depending on where they live. They said that people with the condition would benefit from a longer-term treatment option, because current medicines can only be used for a short time. The committee concluded that long-term insomnia can substantially affect people's quality of life, and there is an unmet need for longer-term treatment options.

Treatment pathway

First-line standard treatment is CBTi

3.2 The company explained that insomnia is often treated in primary care. For short-term insomnia, sleep hygiene advice is offered. After this, medicines such as benzodiazepines, zopiclone, zolpidem and melatonin are used for a short time (less than 4 weeks or less than 13 weeks for melatonin; although some people take them for longer than this). The company highlighted the difference between treatments for short-term insomnia and long-term insomnia. It stated that sleep hygiene advice is also offered for long-term insomnia. Then, cognitive behavioural therapy for insomnia (CBTi) is the recommended first-line treatment. However, currently access to CBTi varies across the country. The clinical experts also noted that there are difficulties accessing CBTi. They explained that there is no data on the use of CBTi in the NHS nationally, but research done in London showed that access to CBTi was very poor. Even when CBTi was available, people with insomnia were often not aware of it. The clinical experts added that CBTi has a 70% to 80% response rate and roughly 50% of people whose condition responds to it experience long-term remission. They also noted that recently, NICE's medical technologies guidance recommended Sleepio, a self-help digital sleep improvement programme based on CBTi for insomnia and insomnia symptoms. But some people may struggle with online CBTi and some people do not have access to it. The committee understood that CBTi is currently the standard first-line treatment for people with long-term insomnia but access to it varies.

Company's proposed positioning of daridorexant

3.3 The company proposed that daridorexant would be used in primary care for long-term insomnia as:

- a second-line treatment option when digital or face-to-face CBTi has been tried but not worked, or as maintenance treatment for managing longer-term symptoms

- a first-line treatment option when CBTi is not available or unsuitable.

The committee's discussion focused on the company's positioning of daridorexant as a first-line treatment option when CBTi is not available or unsuitable. The committee was aware that access to CBTi varies across the country (see section 3.2) and treatment effects may also vary. It understood that this may also be related to the lack of resources to either referral or signposting to CBTi by GPs. One of the clinical experts emphasised that when possible, GPs should be encouraged to explore reasons why CBTi is not available during diagnosis and signpost people to have CBTi treatment first. The committee agreed with the clinical expert. The committee concluded that the company's positioning of daridorexant as a second-line treatment option for long-term insomnia, when digital or face-to-face CBTi has been tried but not worked, or as maintenance treatment for managing longer-term symptoms, was appropriate. It also concluded that positioning daridorexant as a first-line treatment option when CBTi is not available or unsuitable was acceptable. But when available and suitable, CBTi should always be offered first before daridorexant.

Comparator

3.4 The company provided evidence on daridorexant compared with placebo (see section 3.7). Because CBTi should be the first-line treatment when available and if suitable, the committee agreed it was not an appropriate comparator. So it agreed that placebo was the appropriate comparator for decision making.

Diagnosis of long-term insomnia

3.5 The committee noted that daridorexant would be used mainly in primary care by GPs. It discussed how long-term insomnia would be diagnosed by GPs and how this tied in with the population enrolled in the pivotal trial for daridorexant, study 301 (see section 3.7). The clinical experts explained that there are criteria for diagnosis of long-term insomnia, but in practice it

would also be based on patient experience. GPs would assess perception of sleep quality, sleep quantity and any daytime symptoms. The clinical experts also explained that the natural history of insomnia varies across people. Acute insomnia may be resolved in the short term. But once becoming chronic and lasting for more than 6 months, it may last for years and be difficult to resolve. The committee, comprised partly of GPs, discussed the lack of guidance on insomnia in the UK and highlighted the importance of considering differential diagnoses before prescribing medicine for long-term insomnia. The committee understood that the time constraint of a GP appointment can be a barrier to this. The clinical experts also noted that if recommended, daridorexant would be new to primary care. They explained that it would be good to have a longer-term treatment option in primary care. But GPs may not be confident or may be reluctant to start medicines for longer-term use. So, the clinical experts highlighted that, if daridorexant were recommended, support to and training of GPs would be key for its implementation in practice. The committee understood that although there are criteria for diagnosing insomnia, GPs also assess people's experience of the condition, which is subjective. So there may be uncertainties or variations in diagnosis. It also recognised that, if daridorexant were to be recommended, further support and training for GPs about diagnosing long-term insomnia and the available treatment options would be important. This is because daridorexant, if recommended, would be the first medicine available to GPs for the longer-term treatment of long-term insomnia.

Concomitant treatments

3.6 The EAG highlighted that people could have other treatments at the same time as the randomised treatments (concomitant) in the company's pivotal trials, study 301 and study 303. CBTi was allowed if it had been started 4 or more weeks before baseline and continued throughout the studies. Non-prohibited medicines that were part of people's normal care were also allowed. People in both arms did sleep hygiene measures during the study. The committee discussed whether daridorexant, if recommended,

could be used alongside other medicines and non-medicine treatments in practice. The clinical experts explained that adherence to sleep hygiene measures are still important when having medicine. They reiterated that sleep hygiene measures and behavioural changes for people with insomnia are essential to maximise the treatment effect of daridorexant. They also explained that other treatments for insomnia work in a different way to daridorexant, in that they help with falling asleep. Daridorexant, in comparison, also helps with staying asleep. The committee understood that if daridorexant were recommended, ongoing reinforcement of behavioural changes or sleep hygiene would still be necessary and important. It considered that the comparative effectiveness evidence from the trials was appropriate for decision making. The committee concluded that, if recommended, daridorexant could be used at the same time as other medicines or non-medicine treatments available in practice.

Clinical evidence

Clinical effectiveness evidence

3.7 The clinical effectiveness evidence was from study 301 and its extension study, study 303. Study 301 was a phase 3 double-blind randomised controlled trial with 930 people with long-term insomnia randomly assigned to have daridorexant 25 mg (n=310), daridorexant 50 mg (n=310) or placebo (n=310) for 12 weeks. The company only presented evidence for the 50 mg dose of daridorexant compared with placebo in its submission. The double-blind treatment period was followed by a placebo run-out period in which people had once daily single-blind placebo treatment, and then an unblinded safety follow-up period. Key inclusion criteria for study 301 and study 303 were:

- 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 and

- An insomnia severity index (ISI) score of at least 15.

Key exclusion criteria included:

- concomitant CBTi unless started at least 1 month before visit 3 (baseline timepoint) and continued throughout the study
- mental health conditions diagnosed by the Mini International Neuropsychiatric Interview as 'acute or unstable'
- concomitant CYP3A4 inhibitors.

The primary efficacy endpoints in study 301 were change in:

- wake after sleep onset (WASO) from baseline to month 1 and month 3, respectively
- latency to persistent sleep (LPS) from baseline to month 1 and month 3, respectively.

Study 303 was primarily a comparative safety study, but it included placebo-controlled subjective outcomes to assess the long-term maintenance effect of daridorexant. People who had daridorexant 50 mg in study 301 or study 302 (another phase 3 study double-blind randomised controlled trial) continued having the same dose in study 303 (n=137). Those assigned to placebo in study 301 or study 302 were re-randomised to have either placebo (n=128) or daridorexant 25 mg in study 303. 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 for study 303 was the total number of people with at least 1 treatment-emergent adverse event. The committee noted that evidence from study 302, in which 924 people with long-term insomnia were randomly assigned to have daridorexant 10 mg (n=307), daridorexant 25 mg (n=309) or placebo (n=308) for 12 weeks, was not presented. This is because the company only considered evidence for the 50 mg dose of daridorexant relevant for the submission.

Clinical effectiveness results

WASO and LPS

3.8 There were greater reductions from baseline in WASO and LPS for daridorexant 50 mg compared with placebo at both month 1 and month 3 in study 301. For WASO, at month 1 and month 3, daridorexant 50 mg was associated with less wake time after sleep onset from baseline compared with placebo (least squares mean [LSM] difference 22.78 minutes [p<0.0001] and 18.30 minutes [p<0.0001], respectively). Similarly, for LPS, at month 1 and month 3, daridorexant 50 mg was associated with a shorter delay to persistent sleep from baseline compared with placebo (LSM difference 11.35 minutes (p<0.0001) and 11.67 minutes (p<0.0001), respectively. The company explained that these objective measures were used as the primary outcomes for regulatory approval. The clinical experts explained that daridorexant is a medicine for sleep maintenance. They noted that the differences in WASO and LPS can be considered clinically meaningful but emphasised that in practice, subjective improvements in sleep quality, sleep quantity and daytime symptoms are more important than measures such as WASO and LPS.

ISI score

3.9 The ISI score was an exploratory outcome in study 301 and study 303 and was the only efficacy outcome the company used to inform its economic modelling. The ISI has 7 questions and the total score, ranging from 0 to 28, is the sum of the scores for each of the questions. Higher scores indicate a higher severity of insomnia. Reductions from baseline in ISI were greater for daridorexant 50 mg compared with placebo at both month 1 and month 3. At month 1, the reduction from baseline in mean ISI was 4.9 (standard deviation [SD] 5.5) and 3.1 (SD 4.7) for daridorexant and placebo, respectively. At month 3, the reduction from baseline in mean ISI was 7.2 (SD 6.5) and 5.4 (SD 5.7) for daridorexant and placebo, respectively. The EAG did a between-arm analysis for ISI at 3 months,

which showed a mean difference of -1.8 (95% confidence interval - 2.74 to -0.85). The clinical experts commented that a difference of at least 4 in a between-arm analysis for ISI would be considered clinically meaningful but noted that the placebo effect in this case was substantial. They also noted that in clinical practice only people who benefit from treatment would continue, so it can be expected that a larger reduction would be seen in clinical practice. The ISI results from study 303 are considered confidential and cannot be reported here. The committee concluded that daridorexant may be associated with a greater reduction in ISI scores compared with placebo. But there was uncertainty about whether the difference between the 2 arms was clinically meaningful.

Exploratory outcomes

3.10 Some other exploratory outcomes were assessed in study 301 and study 303, including total sleep time, Insomnia Daytime Symptoms and Impacts Questionnaire, Patient Global Assessment of Disease Severity score, Patient Global Impression of Change score and sleep efficiency (%). Between-arm analyses were done for the outcomes by the company and EAG. That is, the mean difference of change from baseline in outcome on daridorexant minus the mean difference of change from baseline on placebo. For most outcomes, daridorexant showed a statistically significant reduction in insomnia compared with placebo at 3 months. But the EAG noted that the benefits of daridorexant compared with placebo at 3 months follow up did not appear to persist at 12 months for some outcomes. The exact outcomes are considered confidential and cannot be reported here. The committee noted that there was no clinical data beyond 12 months. The clinical experts stated that it was difficult to predict long-term treatment effect without data beyond 12 months, but noted that people would stop treatment if they were no longer benefitting. The committee concluded that daridorexant was largely effective in improving symptoms related to long-term insomnia at 12-month follow up, but there are uncertainties about the duration and extent of benefit of treatment beyond 12 months.

Safety results

3.11 In study 301, during the double-blind study period, treatment-emergent adverse events were reported in 37.7% (116 out of 308) and 34.0% (105 out of 309) of people in the daridorexant 50 mg arm and placebo arm, respectively. Treatment-emergent serious adverse events were reported in 1.0% (3 out of 308) and 2.3% (7 out of 309) of people in the daridorexant 50 mg arm and placebo arm, respectively. In study 303, during the double-blind study period, there were treatment-emergent adverse events in 38.0% (52 out of 137) and 33.6% (43 out of 128) of people in the daridorexant 50 mg arm and placebo arm, respectively. Treatment-emergent serious adverse events were reported in 5.1% (7 out of 137) and 1.6% (2 out of 128) of people in the daridorexant 50 mg arm and placebo arm, respectively. The clinical experts commented that the safety effect profile of daridorexant indicates that it is better tolerated than other medicines used for treating insomnia.

Uncertainty in longer-term treatment effect

3.12 The committee was aware that evidence from study 301 and study 303 indicated that daridorexant's treatment effect compared with placebo at 3 months did not appear to persist at 12 months for some outcomes (see section 3.10). There was also no trial evidence on daridorexant's treatment effect beyond 12 months. It questioned whether it could be possible for the treatment effect to taper but still provide some marginal benefit. The clinical experts explained that it is unknown because of the lack of evidence. People would stop treatment if there is no benefit but may still continue if there is some benefit. The clinical experts also explained that some people may neglect sleep hygiene measures while taking medicine, which could affect the treatment effect. But there is a lack of opportunity to find out what behaviours offset the effect of medicines. A clinical expert continued that a 'drug holiday' may also be possible in practice, and some people may continue benefitting from treatment after stopping. The committee agreed that it is important for GPs to reinforce sleep hygiene advice alongside use of medicines in practice. It concluded

that the long-term treatment effect of daridorexant is uncertain and took this into account in its decision making.

Generalisability of evidence to NHS population

Selective enrolment criteria of trials

3.13 The committee understood that the DSM-5 criteria of insomnia disorder was one of the criteria used to enrol people in study 301 and study 303. According to the DSM-5 criteria, insomnia disorder is defined as dissatisfaction with sleep quantity or quality associated with:

- difficulty falling asleep or maintaining sleep
- waking up early without being able to return to sleep
- significant social or functional distress or impairment because of sleep disturbance. Sleep difficulty occurs at least 3 nights a week and happens for at least 3 months despite adequate opportunities for sleep.

The EAG noted that the trial inclusion criteria for study 301 contained specific details on top of the DSM-5 criteria. For example, an ISI score of at least 15, at least 30 minutes to fall asleep, and wake time during sleep of at least 30 minutes. The EAG further added that this could make the trial population narrower than those seen in the NHS. The committee recalled that clinical experts stated that diagnosis of long-term insomnia in practice would also be based on people's experience, which could be subjective. GPs would assess perception of sleep quality, sleep quantity and any daytime symptoms (see section 3.5). The clinical experts added that ISI is not a screening tool so should not be used in clinical practice to diagnose insomnia. The committee concluded that the inclusion criteria for the trial may result in a narrower trial population than the anticipated treatment population, which adds uncertainty to the generalisability of the evidence. It took this into account in its decision making.

Excluding mental health conditions

3.14 Study 301 excluded people with 'acute and unstable' mental health conditions. The company explained that 'acute and unstable' was defined in the trial as any mental health condition needing psychoactive medicine. The committee considered this to be very broad and included many chronic conditions. The EAG noted that insomnia frequently occurs alongside mental health conditions. So excluding people with mental health conditions also results in uncertainty about the generalisability of treatment effect to the anticipated treatment population. The company acknowledged that people with comorbid mental health conditions who need medicine were not included in the trials. This was because it may be challenging to separate the benefits of daridorexant from treatments for mental health conditions. The company added that medicines for mental health conditions are known to affect sleep, have been associated with insomnia and also modulate neurotransmitters involved in the regulation of the sleep-wake cycle. The clinical experts explained that medicines for insomnia can be offered to people with mental health conditions. So they would expect that daridorexant would also be offered to people with mental health conditions. The committee noted the importance of differential diagnoses including chronic, stable and comorbid psychiatric diagnoses. It also noted that people with mental health conditions would likely follow the treatment pathway for their condition first before daridorexant would be considered as a treatment option for long-term insomnia. The committee understood the company's reason for excluding people with mental health conditions from the trials. It noted that daridorexant may be offered to people with mental health conditions in practice. It concluded that excluding people with mental health conditions from trials resulted in uncertainty about the generalisability of the clinical evidence. The committee took this into account in its decision making.

Ethnicity

3.15 Study 301 (n=930) reported ethnic groups as follows: 1% Asian, 9.5% Black and 89.5% White. Study 303 reported ethnic groups as follows: 1%

Asian, 8.5% Black and 89.5% White. The EAG highlighted that there was a possible difference in the proportions of ethnic groups in the UK population of people with long-term insomnia, and the clinical trial populations. The proportions of ethnic groups in the UK population with long-term insomnia do not appear to be available in the literature. So there is uncertainty about whether proportions of ethnicities in the trial are representative of the UK target population. The EAG commented that if ethnicity is a treatment effect modifier for daridorexant, differences in ethnicity proportions between study 301 and study 303, and the UK target population, could potentially affect applicability. Study 301 did not subgroup for ethnicity. Also, while study 303 did not find evidence that ethnicity was an effect modifier, analyses were only presented for 2 outcomes. The company explained that published literature suggested that differences in metabolism between ethnic groups are not clinically significant, so it expects that the treatment effect is not affected by ethnicity. The clinical experts stated that in their experience, response to insomnia medicine is not affected by ethnicity. But study 301 and study 303 did not include people from the UK. A clinical expert stated that behaviours affecting sleep quality could differ between the UK and other European counties. The committee understood that currently there is a lack of evidence on whether ethnicity would modify the treatment effect of daridorexant. It concluded that the difference in the proportions of ethnic groups between the UK population with long-term insomnia and the clinical trial populations adds further uncertainty to the generalisability of the evidence. The committee took this into account in its decision making.

Additional clinical study and evidence on 25 mg dosage

3.16 The EAG was concerned that Dauvilliers et al. (2020), a study comparing daridorexant (5 mg, 10 mg, 25 mg or 50 mg) with placebo was not included in the company's clinical effectiveness results. The company explained that this study assessed the dose–response relationship, so was not designed to evaluate efficacy and safety of daridorexant compared with placebo because of the small sample size. It added that

outcomes were assessed on days 1 and 2 only and not deemed relevant to long-term treatment of long-term insomnia. A clinical expert noted that daridorexant is a new medicine with limited evidence. So, they would consider this study relevant despite the limitations with follow-up time and sample size because it would increase the evidence base. The committee recalled clinical expert opinion that in clinical practice, GPs are likely to start from the lower 25 mg dose and titrate up to the 50 mg dose if needed (see section 3.18). The committee also recalled that study 302 included the 25 mg dose of daridorexant (see section 3.7). The committee concluded that it would like to see evidence on the treatment effect of the daridorexant 25 mg and 50 mg doses from the Dauvilliers et al. (2020) study. It further concluded it would also like to see evidence on the treatment effect of the daridorexant 25 mg dose from study 302 as part of its decision making.

Economic model

Company's modelling approach

3.17 The company presented a de novo economic model and stated that it was not aware of any formal terminology to describe the model form. It used multiple regression models to estimate costs and effects for months 1, 3, 6, 9 and 12 based on observed ISI scores from study 301 and study 303. The company explained that it chose ISI to inform the model because there is a lack of data sources to inform the mapping to EQ-5D for other trial outcomes. The time horizon in the company's base-case model was 12 months. The company also presented a lifetime time horizon scenario analysis which explored the epidemiological relationship between poor sleep and poor long-term health outcomes. This included a mortality benefit for daridorexant and improved cost effectiveness compared with the base case. The company explained that a 12-month time horizon was chosen for the base case because this timeframe corresponds to the combined period of study 301 and study 303. Extrapolating beyond the available data would be based on assumptions, which would add uncertainty. It further stated that the

benefits of daridorexant would apply within hours of starting treatment and are lost within hours of stopping treatment. So a 12-month time horizon is sufficient and appropriate to estimate cost effectiveness while allowing for including dropout rates. The committee understood that long-term insomnia is a chronic condition but the model assessed symptoms related to it as measured by ISI. The committee also understood that there was no evidence on daridorexant's long-term treatment effect (see section 3.10). So the committee accepted a 12-month time horizon for the base-case analysis.

Dosage

3.18 The committee noted that the marketing authorisation for daridorexant includes the 25 mg and 50 mg doses. But the company submission focused on the clinical effectiveness of the 50 mg dose (see section 3.7), and the model included only the 50 mg dose. The company explained that the 25 mg dose is indicated for a subgroup of people with liver problems or who are having CYP3A4 inhibitors. It added that for this subgroup, the 25 mg dose is to achieve '50 mg equivalent' daridorexant plasma levels and that the cost effectiveness is expected to be the same for both doses. The EAG considered that omitting the 25 mg dose presented a problem for population applicability because the results from the trial are not applicable to people with conditions for which the 25 mg dose is indicated (see section 2.2). A clinical expert added that in clinical practice, GPs are likely to start from the lower 25 mg dose and titrate up to the 50 mg dose if needed. The committee acknowledged that the trial data for the 25 mg dose is not applicable to the population for which summary of product characteristics recommends the 25 mg dose. But based on clinical expert opinion, the committee considered that people without liver problems or not having CYP3A4 inhibitors may still start on the 25 mg dose. The committee concluded that it would like to see a scenario analysis for the cost effectiveness of the 25 mg dose.

Model comparators

3.19 The decision problem comparator is established clinical management (ECM). The comparator used by the company in the economic modelling was 'no treatment', with the placebo arm of the trial serving as a proxy for no treatment based on the analysis of study 301 (see section 3.7). The company stated that none of the currently approved medicines are recommended for long-term use. It explained that daridorexant is indicated for long-term insomnia with symptoms for at least 3 months, as per the clinical trial. The company reiterated that the proposed positioning for daridorexant is at second line after CBTi has been tried and not worked, or as a maintenance treatment option for longer-term management of symptoms, or at first line when CBTi is not available or unsuitable. So medicines or CBTi cannot be considered ECM or appropriate comparators. The committee recalled that it considered the company's positioning of daridorexant appropriate (see section 3.3). Based on the company's proposed positioning of daridorexant in the treatment pathway, after CBTi unless CBTi was inaccessible or unsuitable, the committee concluded that 'no treatment' is the appropriate comparator in the model.

Placebo effect

3.20 The ISI scores for both the daridorexant and the placebo arm decreased at each timepoint in study 301 and study 303. The company's base-case analysis only accounted for the placebo effect for the first 3 months. Specifically, it assumed that the no treatment group would continue at the same ISI achieved by the end of study 301 (that is, month 3). The company considered this assumption conservative (compared with ISI scores for the no treatment group dropping to baseline). It also considered that the increasing improvement in ISI scores over time in study 303 could be attributed to selective attrition (the selective dropout of some people who systematically differ from those who remain in the study) in both treatment groups. The company added that the trial data showed that people who dropped out of study 303 before the week 40 visit had smaller

changes in ISI scores compared with those who completed the study, which supported the selective attrition argument. The EAG explained that the company's approach of accounting for placebo effect for the first 3 months was not necessarily conservative and there was uncertainty. The EAG commented that it was unclear whether the improvement in ISI scores over time could be attributed to natural improvement of symptoms, regression to the mean, or the placebo effect. It added that despite a rebound effect between the end of study 301 and beginning of study 303, study 303 continued for 40 weeks more and scores could have improved naturally, especially given that insomnia is highly related to lifestyle factors. In its base case, the EAG preferred to include placebo adjustment for the time horizon of 12 months based on ISI scores in both study 301 and study 303. The committee considered that selective attrition might be a possible explanation for the improvement in ISI scores. But it was not presented with evidence supporting this argument. The committee understood that the EAG considered that the improvement in ISI score could also be caused by natural improvement of symptoms, regression to the mean or the placebo effect. Given the uncertainties, the committee concluded that it preferred the EAG's base-case assumption, which used the ISI scores from both study 301 and study 303 to inform the ISI for the no treatment group. It acknowledged that selective attrition might be possible, but it would like to see additional data or evidence to support this argument.

Stopping treatment

3.21 The committee noted that the summary of product characteristics for daridorexant does not include a stopping rule. However, it states that treatment duration should be as short as possible, with check-ups within 3 months and periodically after. The committee noted that study 303 reported that about less than 10% (the exact data is considered confidential so not reported here) of people on daridorexant 50 mg stopped because of lack of treatment effect. It also noted that in the company's analysis based on patient level data from the trials, a relatively

large proportion of people (the data is considered confidential so not reported here) dropped out from the daridorexant arm at 12 months. The committee recalled the discussion about daridorexant's longer treatment effect (see section 3.12) and the uncertainties related to it. The committee was also aware that there are not many secondary care sleep services in many parts of the UK. Given this lack and the uncertainty in daridorexant's long-term treatment effect, the committee considered that exploring stopping daridorexant, which will be mainly used in a primary care setting, would be important. The committee concluded that it would prefer to see analyses exploring treatment effect waning, as well as a stopping rule in the company's lifetime time horizon scenario.

Adverse events

3.22 The company's economic model did not include adverse events. This was based on the company's opinion that adverse events were not expected to significantly affect health-related quality of life and costs. The EAG stated that it did not expect a large impact on cost-effectiveness results but would prefer all adverse events from study 301 and study 303 to be included in the cost-effectiveness analysis. The committee concluded that the effect of including adverse events in the model is likely to be minor. But it would prefer the estimated impact of adverse events on costs and quality-adjusted life years (QALYs) to be included in the economic model.

Utility values

3.23 The company developed a novel mapping algorithm based on the National Health and Wellness Survey (NHWS) dataset to map ISI data from study 301 and study 303 to EQ-5D values. The company stated that ISI was used because there were no available data sources to estimate a mapping function for other trial outcomes. The company's base-case model used an adjusted limited dependent variable mixture model to create the mapping function. This model narrowly out-performed a generalised linear model with a gamma distribution family and log link function based on model fitting performance and predictive validity. The

EAG was concerned with the lack of a conceptual overlap between ISI and EQ-5D instruments, and the subsequent suitability of the mapping algorithm to estimate health-related quality of life in insomnia. The EAG also had concerns that the population used for developing the mapping algorithm (from the NHWS survey) was broader than the trial population. The company responded that ISI correlates with EQ-5D and was suitable to estimate QALYs. It added that it is very plausible that the EQ-5D does not fully capture the effect of long-term insomnia on health-related quality of life, so QALY benefits may be underestimated. Regarding the comparability of populations for developing the mapping algorithm, the company stated that the broader range of severity from the NHWS survey than in the clinical trial could be argued as a positive attribute. This is because a broader range of ISI and EQ-5D values should result in a more robust mapping algorithm. The committee concluded that the utility values presented by the company were appropriate for decision making but noted the uncertainties in mapping. It took this into account of its decision making.

Costs

3.24 The company's economic model included treatment costs and medical costs (GP visits, emergency room attendances and inpatient care). To estimate the resource use for medical costs, the association between direct healthcare resource use (GP visits, emergency room attendances and inpatient care) and ISI scores were calculated from the NHWS data. This was done using a generalised linear model with a negative binomial distribution family and a log link. The EAG stated that it would prefer all relevant costs to the NHS and personal social services to be included in the economic model. For example, the company did not include concurrent medication costs and outpatient care costs. The committee agreed that including only costs related to GP visits, emergency room attendances and impatient care was a conservative assumption. Further, the committee recalled the discussion (see section 3.5) that, if daridorexant were recommended, further support and training for GPs

would be needed for diagnosing long-term insomnia in primary care. The committee also recalled that reinforcement about currently available treatment options would be important to ensure daridorexant's effective use in primary care. So, the committee concluded that it would prefer all costs incurred by the NHS, including providing support and training for GP practices, to be included in the economic model.

Cost-effectiveness estimates

Uncertainties in evidence and model assumptions

3.25 The committee noted the high level of uncertainty in the company's clinical evidence and model assumptions, specifically the:

- uncertainty in whether the difference from baseline in ISI scores between the 2 arms was clinically meaningful (see section 3.9)
- lack of evidence about daridorexant's longer-term treatment effect, including uncertainties in treatment duration as well as extent of benefit of treatment beyond 12 months (see section 3.12 and section 3.21)
- trial populations being narrower than the anticipated treatment population (see section 3.13)
- generalisability of evidence from study 301 and study 303 to UK practice in terms of excluding people with mental health conditions and non-UK based trial locations (see sections 3.14 and 3.15)
- uncertainty about whether ethnicity is a treatment effect modifier for daridorexant, and the proportion of ethnic groups in trials not representing that of the UK population with insomnia (see section 3.15)
- omission of study results from Dauvilliers et al. (2020) and evidence on the clinical effectiveness of daridorexant 25 mg not presented (see section 3.16)
- 25 mg dose of daridorexant not assessed in the economic model (see section 3.18)
- uncertainty about whether the improvement in ISI in the placebo arm of study 303 was a result of selective attrition, natural improvement of

symptoms, regression to the mean or the placebo effect (see section 3.20)

- adverse events not being included in the economic analyses (see section 3.22)
- uncertainty associated with the mapping of ISI to EQ-5D (see section 3.23)
- not all relevant costs to the NHS and personal social services being included in the model, for example, costs to provide support and training for GP practices (see section 3.24).

Uncertainty in cost effectiveness and more analyses needed

3.26 NICE's manual for health technology evaluations notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the incremental cost-effectiveness ratio (ICER). The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. Because the list price of daridorexant is not yet approved, the ICERs are commercial in confidence and cannot be reported here. But the committee noted that the cost-effectiveness estimates including some of its preferred assumptions were above the range NICE normally considers to be an acceptable use of NHS resources. Neither the company nor the EAG's base cases or scenario analyses included all the committee's preferred assumptions. The committee considered that further analyses are needed. It requested:

- including the evidence on the treatment effect of daridorexant 25 mg from study 302; and evidence on the treatment effect of daridorexant 25 mg and 50 mg from the Dauvilliers et al. (2020) study (see section 3.16)
- estimating the cost effectiveness of the 25 mg dose of daridorexant in the economic analysis (see section 3.18)
- providing additional evidence or data that supports the argument of selective attrition (see section 3.20)

- exploring treatment effect waning and stopping treatment in the lifetime horizon scenario analysis (see section 3.21)
- including the impact of adverse events on costs and QALYs in the model (see section 3.22)
- all costs that would occur in the NHS in the model, including the costs to provide support and training for GPs (see section 3.24).

Other factors

Equality issues

3.27 The company noted that that CBTi is recommended as first-line treatment for long-term insomnia but may not be suitable for or accessible to all people. The committee recognised this and understood that care varied, with people having different standards of care for long-term insomnia depending on where they live in the country. But the committee noted that access to treatments is an implementation issue that cannot be addressed by a NICE technology appraisal recommendation. No other equality or social value issues were identified.

Innovation

3.28 The company considered that daridorexant is innovative. This is because the current medicines are recommended only for short-term use, and daridorexant is a longer-term option. Also, daridorexant is the first dual orexin receptor antagonist approved in the UK and Europe for treating long-term insomnia. The company also explained that there may be uncaptured benefits in its base-case analysis, because daridorexant may reduce the risk of cardiovascular disease and mortality in people with insomnia in the longer term. The committee concluded that there might be additional benefits with daridorexant. But, given the uncertainties in the evidence and in the model (see section 3.24), it was unclear whether there were any not captured in the cost-effectiveness analysis.

Conclusion

Recommendation

3.29 The committee considered the most plausible ICER available and took into account the degree of certainty around the ICER. The most plausible ICER was above the range NICE normally considers cost effective. It concluded that it was not possible to recommend daridorexant for treating long-term insomnia in adults.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Charles Crawley

Chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Dilan Savani

Technical lead

Yelan Guo

Technical adviser

Daniel Davies

Project manager

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